AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

APRIL 29, 2008

Serial No. 110–109

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES

THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

APRIL 29, 2008

Serial No. 110–109

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PRINTING OFFICE
53–183 PDF WASHINGTON : 2008

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON ENERGY AND COMMERCE

JOHN D. DINGELL, Michigan, *Chairman*

HENRY A. WAXMAN, California
EDWARD J. MARKEY, Massachusetts
RICK BOUCHER, Virginia
EDOLPHUS TOWNS, New York
FRANK PALLONE, JR., New Jersey
BART GORDON, Tennessee
BOBBY L. RUSH, Illinois
ANNA G. ESHOO, California
BART STUPAK, Michigan
ELIOT L. ENGEL, New York
ALBERT R. WYNN, Maryland
GENE GREEN, Texas
DIANA DeGETTE, Colorado
Vice Chairman
LOIS CAPPS, California
MICHAEL F. DOYLE, Pennsylvania
JANE HARMAN, California
TOM ALLEN, Maine
JAN SCHAKOWSKY, Illinois
HILDA L. SOLIS, California
CHARLES A. GONZALEZ, Texas
JAY INSLEE, Washington
TAMMY BALDWIN, Wisconsin
MIKE ROSS, Arkansas
DARLENE HOOLEY, Oregon
ANTHONY D. WEINER, New York
JIM MATHESON, Utah
G.K. BUTTERFIELD, North Carolina
CHARLIE MELANCON, Louisiana
JOHN BARROW, Georgia
BARON P. HILL, Indiana

JOE BARTON, Texas
Ranking Member
RALPH M. HALL, Texas
FRED UPTON, Michigan
CLIFF STEARNS, Florida
NATHAN DEAL, Georgia
ED WHITFIELD, Kentucky
BARBARA CUBIN, Wyoming
JOHN SHIMKUS, Illinois
HEATHER WILSON, New Mexico
JOHN B. SHADEGG, Arizona
CHARLES W. "CHIP" PICKERING, Mississippi
VITO FOSSELLA, New York
STEVE BUYER, Indiana
GEORGE RADANOVICH, California
JOSEPH R. PITTS, Pennsylvania
MARY BONO, California
GREG WALDEN, Oregon
LEE TERRY, Nebraska
MIKE FERGUSON, New Jersey
MIKE ROGERS, Michigan
SUE WILKINS MYRICK, North Carolina
JOHN SULLIVAN, Oklahoma
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee

Professional Staff

Dennis B. Fitzgibbons, *Chief of Staff*
Gregg A. Rothschild, *Chief Counsel*
Sharon E. Davis, *Chief Clerk*
David L. Cavicke, *Minority Staff Director*

Subcommittee on Oversight and Investigations

BART STUPAK, Michigan, *Chairman*

DIANA DeGETTE, Colorado
CHARLIE MELANCON, Louisiana
Vice Chairman
HENRY A. WAXMAN, California
GENE GREEN, Texas
MIKE DOYLE, Pennsylvania
JAN SCHAKOWSKY, Illinois
JAY INSLEE, Washington
JOHN D. DINGELL, Michigan *(ex officio)*

ED WHITFIELD, Kentucky
Ranking Member
GREG WALDEN, Oregon
MIKE FERGUSON, New Jersey
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee
JOE BARTON, Texas *(ex officio)*

CONTENTS

Page

Hon. Bart Stupak, a Representative in Congress from the State of Michigan, opening statement 1
Hon. John Shimkus, a Representative in Congress from the State of Illinois, opening statement 4
Hon. John D. Dingell, a Representative in Congress from the State of Michigan, opening statement 6
Hon. Michael C. Burgess, a Representative in Congress from the State of Texas, opening statement 8
Hon. Jan Schakowsky, a Representative in Congress from the State of Illinois, opening statement 10
Hon. Joe Barton, a Representative in Congress from the State of Texas, prepared statement 179
Hon. Gene Green, a Representative in Congress from the State of Texas, prepared statement 180

WITNESSES

David Nelson, Senior Investigator, Committee on Energy and Commerce, Washington, DC 12
  Prepared statement 14
Colleen Hubley, Toledo, Ohio 17
  Prepared statement 19
Leroy Hubley, Toledo, Ohio 20
  Prepared statement 21
Johanna Marie Staples, Toledo, Ohio 22
  Prepared statement 23
Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland; accompanied by Deborah M. Autor, Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland; and Regina T. Brown, Consumer Safety Officer, Division of Field Investigations, Office of Regional Operations, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland 44
  Prepared statement 47
Robert L. Parkinson, Jr., chairman, chief executive officer and president, Baxter International, Inc., Deerfield, Illinois 98
  Prepared statement 100
David G. Strunce, chief executive officer, Scientific Protein Laboratories, LLC, Waunakee, Wisconsin; accompanied by Yan Wang, Ph.D., vice president of business development and research, Scientific Protein Laboratories, LLC, Waunakee, Wisconsin 120
  Prepared statement 122
Clive Meanwell, M.D., chairman and chief executive officer, The Medicines Company 159
  Prepared statement 161

SUBMITTED MATERIAL

Slides accompanying Mr. Stupak's presentation 182
Letter of June 2, 2008, from the Food and Drug Administration to Hon. Bart Stupak 187
Heparin patent application 191
Subcommittee exhibit binder 196

THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES

TUESDAY, APRIL 29, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to call, at 11:04 a.m., in room 2123, Rayburn House Office Building, Hon. Bart Stupak (chairman of the subcommittee) presiding.

Present: Representatives Stupak, Melancon, Schakowsky, Inslee, Dingell (ex officio), Shimkus, and Burgess.

Staff Present: Scott Schloegel, John Sopko, David Nelson, Kevin Barstow, Calvin Webb, Chris Knauer, Kevin Chapman, Elizabeth V. Barrett, Alan Slobodin, and Peter Spencer.

OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. This meeting will come to order.

Today we have a hearing entitled, “The Heparin Disaster: Chinese Counterfeits and American Failures.”

Each member will be recognized for a 5-minute opening statement, and I will begin.

Today this subcommittee is holding another in a series of hearings examining the adequacy of the efforts of the Food and Drug Administration to protect Americans from unsafe drugs. Today’s hearing will focus on the circumstances surrounding the recent catastrophe caused by the contamination of the drug heparin. To date, contaminated heparin has been linked to at least 81 deaths and hundreds of severe allergic reactions in the United States.

Today we will hear from two companies responsible for introducing the contaminated heparin into the United States. We will also hear from the FDA regarding the circumstances that led to the introduction of the contaminated heparin and its action after the outbreak was discovered. Finally, we will hear from family members of victims who died after being treated with heparin.

To understand how and why this outbreak occurred, it is first necessary to understand what heparin is, how it is made, and where it is made. Heparin is an important anticoagulant, or blood thinner, that is widely used in surgery and dialysis. It is derived from pig intestines and has been marketed in the United States since the 1930s.

heparin is a natural product that exists in the lining of the pig’s blood vessels. Membrane of the intestine are collected and processed to form a dried substance known as crude heparin. Crude heparin is then further refined and made into an active pharmaceutical ingredient, API, that is sold to drug companies that manufacture the final product.

It is now estimated that China produces over half of heparin's active pharmaceutical ingredients. Indeed, all of the tainted heparin in this case was manufactured from API produced in China.

Baxter, the final manufacturer of the contaminated heparin, has a complex international supply chain shown on the slide we have up on the screens. Their supply chain starts in China, where 10 to 12 Chinese workshops make crude heparin. This crude heparin is then either sold to middlemen called brokers or sold directly to two companies that consolidate the product.

These consolidators then sell the crude heparin to Scientific Protein Laboratories. It is an American company with a plant in Changzhou, China. SPL, Scientific Protein Laboratories, also has a plant in Wisconsin that produces heparin API from the crude heparin. This heparin API is then sold to Baxter, another American company, which manufactures finished heparin products at its Cherry Hill, New Jersey, plant.

In November 2007, Children's Hospital in St. Louis, Missouri, began noticing adverse reactions in their dialysis patients. On January 7, 2008, the Missouri Department of Health and Senior Services notified the Centers for Disease Control and Prevention, who, in turn, notified the FDA and Baxter of the cluster of adverse events.

On January 17th, almost 3 months later, Baxter, which produced about 50 percent of the heparin used in the United States, initiated an urgent nationwide recall of nine lots of heparin products after there was an increase in adverse reactions patients suffered while being given heparin products.

On February 11th, FDA announced that Baxter had halted manufacture of multi-dose vials of heparin because of serious allergic reactions and low blood pressure in patients. On that same day, FDA announced that approximately 350 adverse events associated with heparin had been reported since the end of 2007, and the FDA classified 40 percent of these events as serious, including four deaths. Days later, Baxter recalled all of its heparin injection and solution products remaining on the U.S. market.

As of today, there have been 81 deaths and at least 785 severe allergic reactions associated with heparin since January 2007. Sixty-two of these deaths occurred between November of 2007 and February of 2008.

FDA's investigation into the cause of the outbreak revealed that heparin API made by Changzhou SPL contained a contaminant called oversulfated chondroitin sulfate. Chondroitin sulfate is made from animal cartilage and is cheaper than raw heparin. By itself, chondroitin sulfate does not have blood-thinning properties. However, it can be chemically altered to form oversulfated chondroitin sulfate, which mimics real heparin and is less expensive.

Because oversulfated chondroitin sulfate mimics heparin, it was not detected by standard tests. Oversulfated chondroitin sulfate is not an approved drug in the United States, and it should not have been present in heparin. In samples collected from Changzhou SPL in China, FDA found that this contaminant was present in amounts ranging from 2 to 50 percent of the total content of the API. The contaminant was also found in some of Baxter heparin lots associated with adverse reactions.

To date, it is not known whether this contaminant entered the supply chain accidentally or was introduced intentionally. Because oversulfated chondroitin sulfate is not normally found in nature and is produced through chemical modification, evidence would suggest that this contaminant was intentionally introduced at some stage in the supply chain.

While FDA must be applauded for its outstanding efforts in responding to this outbreak, it must also be held accountable for one glaring and fatal mistake: in 2004, a series of FDA blunders resulted in an FDA decision to approve Changzhou SPL to sell heparin HBI to Baxter without first the FDA conducting a pre-approval inspection of Changzhou SPL's production plant, as is the FDA's policy. This plant was not registered in China as a drug manufacturer, and Chinese officials had never inspected the plant either.

If FDA had conducted such an inspection in 2004, would they have concluded that Changzhou SPL was not capable of meeting current good manufacturing practices, as was concluded by the FDA's inspection after heparin deaths?

It was not until February 20th that the FDA began an inspection of the Changzhou plant. In that inspection, FDA determined that Changzhou SPL was incapable of providing safe heparin API to the United States.

We may never know whether an FDA pre-approval inspection would have prevented this outbreak from occurring. However, it is regrettable that FDA did not inspect this plant sooner, as this may have positively impacted the events related to the heparin tragedy we are discussing today.

While this subcommittee's ire regarding the safety of drugs in this country has been directed toward the FDA, perhaps a greater responsibility to ensure the safety of drugs in this country lies with the drug companies themselves. Make no mistake about it: both Baxter and SPL have failed the American public.

One only needs to look at the FDA's inspection report of Changzhou SPL, which revealed, and I quote, "significant deviations" from U.S. current good manufacturing processes in the production of heparin API. FDA found that Changzhou SPL's processing steps provided no assurance that they were capable of removing impurities. It found that SPL failed to have adequate systems for evaluating both the crude heparin and the suppliers of crude heparin to ensure that their product was acceptable for use. FDA found that the test methods performed by SPL had not been verified to ensure suitability under actual conditions of use. Finally, FDA found that equipment SPL used to manufacture heparin was unsuitable for its intended use.

These findings raise several questions. Why was Baxter obtaining a drug product from a facility that the FDA found to be unsuitable? What due diligence did Baxter or SPL perform before they began using this plant to confirm that it could safely make heparin API for the U.S. market? Why did Baxter sell ingredients from this plant when it knew it had never been inspected by the FDA or China? Why did Baxter buy ingredients from a country that provided little oversight and had a history of producing contaminated products?

These questions in this case are endless. Hopefully some of these questions will be answered today and that these questions will help this committee to continue to move forward in our quest to fix our country's broken drug safety system. Today we look forward to examining what steps must be taken to strengthen this broken system.

I would like to thank all the witnesses for appearing here today, especially the family members who lost loved ones. I'm deeply sorry for your losses; you have suffered. And I appreciate you having the courage to testify before this committee in these very, very difficult times.

That concludes my opening statement. I would next like to turn to the gentleman to my left, the ranking member of the subcommittee, Mr. Shimkus from Illinois, for an opening statement, please, sir.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman.

Last week, this subcommittee focused on the Food and Drug Administration's serious shortcomings in ensuring the safety of drug products imported into the United States. We examined how the system has broken down. We discussed its misplaced priorities, its obsolete information technology, and its resources-starved bureaucratic culture which has failed to confront the serious global challenges warned about for over a decade now.

These shortcomings relate directly to the topic of today's hearing: the contamination, very likely purposeful contamination, of Chinese-source heparin.

As we take testimony today, we should not forget the FDA's shortcomings are not new. Eight years ago, this subcommittee held hearings on counterfeit bulk drugs, focusing on the cluster of adverse events in the U.S. associated with gentamycin ingredient from China. Those hearings highlighted the need for greater scrutiny of drug ingredients, the need for better data, and the possible need for legislation to fix these issues.

The FDA had been on notice about these shortcomings for a long time. And I want to add, had we had moved then, maybe we wouldn't be in this position today.

Much of the agency's problems are institutional, which did not change from administration to administration. Certainly the current administration could have done more, but the reality is its predecessor could have done more, too. Congress has to do its part to push harder for institutional change, to provide the necessary resources and to ensure FDA sticks to its mission. I believe this subcommittee's bipartisan work is helping that effort.

Today we start with the human face of what happens when safeguards fail. And I thank the Hubleys and Ms. Staples for coming to talk to us this morning. This must be difficult and painful, but you remind us why we are working to improve the system. And thank you.

When the drug safety system fails, people get sick. Some die. Some of these people are already very vulnerable, and proving the cause of harm from impurities, adulteration, and counterfeits can be elusive. It is hard to detect harm. Heparin required dramatic statistical spikes in adverse event reports before problems were recognized. That is why information technology is going to be so important.

And I also want to applaud Children's Hospital, which I have visited numerous times since I live right outside the St. Louis area, for their being able to identify problems. And I want to give them credit.

This is why we have to have confidence in our underlying safety standards and systems, and that is also why we need an agency and manufacturers that can anticipate potential vulnerabilities to prevent tragedy.

Today we examine the Chinese heparin contamination which has been associated with hundreds of adverse reactions in patients and scores of deaths. The evidence so far suggests that contamination was a deliberate act by as-yet-identified parties to cut the raw heparin being processed with a substitute that would pass through the standard purity test. It happens to have been driven by economics, the price, and the availability of pigs in China.

I have learned in this investigation that FDA inspectors look for a culture of quality at manufacturing facilities. The FDA foreign surveillance inspections are supposed to help encourage and ensure this culture if they happen frequently enough. Certainly the companies are obligated to ensure a culture of quality and maintain vigilance as well. This reflects a systems approach to safety.

The evidence we will examine today suggests this system approach wasn't at play here. FDA policies led to the failure to inspect the Chinese plant. Baxter, which marketed the heparin, inspected the plant for the first time just this past fall. After several years of operation, this lack of oversight provided more fertile ground for the shenanigans and the heparin counterfeits to flourish. FDA did a good job after the contamination, but that was too late.

This brings me to China and its quality culture or lack thereof. I understand China has been working more closely with the FDA to address concerns about its quality system. This is a positive step. But we hear also that China, while it doesn't deny the counterfeit source, tries to say that counterfeits didn't cause the reaction, as if the adulteration itself was no big deal. Is this an acceptable mindset? Is this going to change any time soon? I hope we see some change through the FDA's new agreements with China.

We have to recognize the enormity of the foreign drug problem, one that is growing and one that may take a long time to solve. But lessons from the heparin contamination should help us understand some of the steps we have to be taking going forward.

Let me thank the witnesses. And let me especially thank Dr. Clive Meanwell, who will appear on the fourth panel today. He brings a knowledge of heparin, the global drug marketplace generally, and a perspective on regulation and motivation we think will contribute to the broader subject matter raised by the heparin case.

And, Mr. Chairman, I want to particularly thank you and your staff for allowing Mr. Meanwell to be in the fourth panel and accommodating our request for this broader perspective.

And with that, I yield back my time.

Mr. STUPAK. I thank the gentleman.

And, as you said earlier, this has been a bipartisan investigation. We are working on our Nation's safety and drug supply. So hopefully our legislation will be bipartisan and we can move that along, also, in the same manner and method.

With that, I next turn to the Chairman of the full committee, Mr. Dingell, for an opening statement, please.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy, and I thank you for holding this hearing and for doing a superb job of leading this investigation into the ability of the Food and Drug Administration to assure the safety of prescription medications from foreign sources.

I would hope, Mr. Chairman, that because of your outstanding leadership on this matter and because of what I see on the part of Members on both sides of the aisle, this will lead us to a hope that we will have strong bipartisan legislation to correct some very serious failures in funding of FDA and inadequacies of its budget and its ability to carry out its mission.

Today we will continue to examine the tragedy of contaminated heparin, which killed some 81 of our citizens and made hundreds, if not thousands, of people very sick in the United States and in other countries around the world.

heparin is a blood-thinning drug given to people receiving dialysis or undergoing open-heart surgery, people whose health is already compromised and for whom contaminated drugs pose potentially fatal consequences. Doctors, hospitals, and clinics have administered millions of doses of this drug in the belief that it was safe and that no one would be endangered by contamination or other failures in the delivery system. And none believed that it would cause a critical allergic reaction.

Baxter Health Care, which manufactured the drug, supplies many patient-care items to hospitals, but there was no label that indicated to doctors, hospitals, or their patients that the active ingredient in heparin was made in China, a country with an extremely unreliable drug or food safety regime, as noted by many experts and confirmed in the hearings of this committee.

Baxter knew the heparin ingredients came from China. We assume, however, that they and other American firms that owned the Chinese plant had no warning that criminals in China were capable of substituting an inexpensive counterfeit ingredient into the production process that mimicked heparin's properties so closely that it was undetectable by standard tests used to determine the purity in drug products.

It should be noted that this exercise appears to have been conducted by the Chinese in connection with other kinds of substances delivered to the United States under the jurisdiction of FDA. And, in other instances, it was impossible to catch the misbehavior because of the way the substance mimicked the substance which it was supposed to replace so closely that it could not be caught.

Here, certainly the FDA, the Government agency responsible for assuring safety of Americans' prescription drug products, had no idea that this supply of heparin contained a deadly contaminant until reports of adverse events started to soar upwards.

Today we seek actions and answers as to whether these companies or FDA should have been able to prevent the situation. Could they have anticipated the actions that led to these counterfeits? Were they receiving proper cooperation from the Chinese? Did they have the proper authorities and the proper abilities to catch the kind of wrongdoing which we see here?

Our investigations so far have revealed that FDA is, here again, woefully lacking in personnel, effective policies, adequate resources, proper funding, and, regrettably, the will at the highest level to perform the duties entrusted to it by the Congress and the American people. That includes procuring adequate funding and informing the Congress of the needs of the agency, something in which FDA is exquisitely deficient.

Our citizens can no longer trust that their food, drugs, or medical devices are safe when the FDA says they are, because they can no longer trust FDA.

I was disappointed last week by the FDA Commissioner's unwillingness to provide us with the cost of properly conducting foreign inspections. And he has not made the case that a proper effort is being made by FDA to secure either the resources, money, or authorities needed to get foreign inspections or the cooperation of foreign countries.

Let us make no mistake: FDA has a dedicated workforce, dedicated public servants who do their best to keep their fingers in the dike. And we commend them for their efforts, and we respect them for their diligence and for their decency. One such employee is with us today, Regina Brown, the FDA investigator who inspected the Changzhou SPL plant last February.

I hope this hearing, as well as the legislation that this committee is now working on, which I hope will be enacted this year and which I hope will be done with bipartisan cooperation, will not only protect the American people but will ensure that those dedicated FDA employees who serve on the front line are able to do the jobs more completely and effectively because they are supported by the leadership at FDA and because they are supported by an administration and a Congress that sees that they have the adequate funds and resources to do their job.

I thank you, Mr. Chairman, and I yield back the balance of my time.

Mr. STUPAK. I thank the Chairman.

Mr. Burgess for an opening statement, please.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Chairman Stupak. And thank you, once again, for holding a hearing and conducting this investigation.

And today, of course, we are trying to better understand what I believe is one of the fundamental purposes of the Federal Government; that is, the safety and security of Americans.

I want to thank all of our witnesses today. I know this is not going to be easy for some of them. I want to thank all of our witnesses, the families, the companies, the Food and Drug Administration, and Dr. Meanwell. I think you will all provide an important link to the story.

And, Dr. Meanwell, although you are at the end of several panels, I think it will be your very detailed and thorough testimony, at the end of the day, that ties much of this together. You provide a valuable historical perspective for the issue that we are going to be discussing today.

This year, we have had hearing after hearing after hearing regarding the resources, or lack thereof, of the Food and Drug Administration. We have also had many important investigations: the heparin issue that we are discussing today; the melamine scandal of last year; and the ongoing investigation regarding dental devices. And, once again, I do thank the leadership of this committee for examining and bringing to the forefront these issues. This committee is also discussing legislation that will reform the authority of the Food and Drug Administration.

While I cannot agree with all of the provisions in the Chairman's FDA Globalization Act, I do welcome an open and honest discussion about the legislation that will transform the system.

We are going to hear testimony today about some fault that may lie with manufacturers. We are going to hear testimony today about some fault that lies with the Food and Drug Administration. What we are probably not going to hear about today is testimony that would revolve around the fault of the United States Congress.

And I want to reference an article in the New England Journal of Medicine from April 24th. It is titled, "Playing 'Kick the FDA': Risk-Free to Players but Hazardous to Public Health."

And quoting from this article, "The fundamental problem is that legislators have heaped more and more responsibility on the Food and Drug Administration without appropriately increasing its budget. Between 1988 and 2007, additional Food and Drug Administration responsibilities were imposed by 137 specific statutes, 18 statutes of general applicability and 14 Executive orders. At the same time, the Food and Drug Administration received a 2007 Federal appropriation of $1.57 billion, less than three-quarters of the budget for the school district in its home county in Maryland," closed quote.

Now, this hearing should include enhancing the FDA's import alert system and give the Food and Drug Administration a true mechanism to stop products that are dangerous from coming into our country and entering our ports.

I have introduced separate legislation, H.R. 3967, the Imported Food Safety Improvement Act of 2007, to do just this in regards to food safety. And I look forward to working with the Chairman to incorporate this idea for active pharmaceutical ingredients that we are discussing today.

And today we are seeking answers, answers regarding the contamination of heparin. And heparin is a drug, in my previous life as a physician, I used to administer to my patients.

And that is why testimony today is so poignant. And we are going to hear testimony from Johanna Staples, and I just want to quote from her testimony, when talking about, at the dialysis center, a procedure of administering heparin, the procedure was deemed to be successful, so he was given a bolus of heparin and his treatment resumed. Think of the poor individual who actually administered the shot—the doctor or the nurse, the attendant. They are going to carry this information around for the rest of their lives, as well.

And it is almost unconscionable that we could have a product that is so distorted from its original intent imported into this country. Now, we are also going to be seeking answers to the safety of the workshop in the People's Republic of China. And you have to ask yourself: is this just an unscrupulous merchant with his thumb on the scale, or is this an activity with malice aforethought done to conflict harm and damage on American patients, and indeed patients worldwide because the European Union and Australia were similarly affected by this?

But most importantly, we are trying to get answers to get to the core value of this country, answers to the most basic and fundamental role of the Federal Government. How do we keep Americans safe and secure? When will people, when will food, when will drugs, when will toys be safe again? This committee, which has jurisdiction over these matters, must answer these questions, and we cannot abdicate our responsibility.

We have had hearing after hearing on the situation. It doesn't come any closer to resolution; it only seems to get worse. We all know the Food and Drug Administration, which should be the premier Federal agency, has been underfunded for decades throughout many administrations and many Congresses, both Republican and Democratic. However, I don't think it has ever been so clear that more resources are needed in order to get Americans to the point of being safe and secure. The resources must be wisely invested, but they must be increased.

And while this committee, Mr. Chairman, doesn't appropriate the money, every single member of this committee knows that this year in Congress we will be lucky if we pass one or two appropriations bills, likely Defense, likely Veterans, which is appropriate and we should do those things, but the appropriation for Health and Human Services not so much. So that appropriation will go through a continuing resolution and likely have level funding for next year.

And what this means is that, as much as we engage in brave discourse about how the Food and Drug Administration needs more resources, it is not going to happen. All of these hearings will be full of sound and fury but, in the end, signifying nothing. And that, frankly, Mr. Chairman, I cannot accept.

I call on the leadership of this committee, the leadership of the Appropriations Committee and Speaker Pelosi to come together to develop a plan to get critical resources to this important agency. If we don't do this, then I think we all know the answer to this question: is protecting the public a top priority, or is it the priority simply to win in November?

I am afraid that I am going to lose my bedside manner, so I am going to yield back the balance of my time. But I do appreciate the Chairman bringing this discussion forward, because it is so critical that we involve ourselves at this level. And I yield back the balance of my time.

Mr. STUPAK. I thank the gentleman.

And, as the gentlemen know, the Dingell-Pallone-Stupak bill provides not only new authority but also the resources for the FDA to do their job, even though the FDA will not tell us the resources they need to do their job, the Dingell bill certainly will do that.

There is a hearing Thursday, and I believe it is before your subcommittee, on that bill, so we can begin that markup, so we can move that legislation. So I thank the gentleman for bringing that to our attention.

Mr. BURGESS. If the gentleman will yield, authorization is critical, but if we don't follow through with an appropriation, then what have we done at the end of the day?

And I will yield back.

Mr. STUPAK. Right. And in our legislation—I don't mean to debate it here this morning, and before I turn to Ms. Schakowsky—we do provide the resources, but we don't think the resources should come from U.S. taxpayers, but from these drug companies that are bringing these APIs, active pharmaceutical ingredients, from foreign areas into this country. They have a responsibility, also have a responsibility, to properly fund FDA to do their job, just as much a responsibility as the U.S. Congress.

So hopefully we can get that resolved, and we invite you to participate in that hearing on Thursday.

And with that, I would turn to Ms. Schakowsky, please, for questions—oh, I am sorry, not questions—opening statement.

OPENING STATEMENT OF HON. JAN SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

The consequences of the contamination of the drug heparin have been truly tragic. I want to sincerely thank the family members of those who fell victim to this crime for being here today and testifying before our subcommittee. We really appreciate you being here.

heparin, as well as many other innovative drugs and biologics that have come to us in the past few decades, have made great contributions to medical care in this country. Unfortunately, with great innovation and the use of cutting-edge medical technology, also comes a certain vulnerability to corruption and exploitation. The heparin disaster is just another in a line of dangerous prescription drug events that have exposed vast weaknesses in how we regulate drug safety in this country.

Thanks to the leadership of Chairman Dingell and the Chairman of our subcommittee, Mr. Stupak, we have learned a lot about what we can do to strengthen regulation and oversight at FDA and reinforce its presence overseas. My hope is that these hearings will also provide us with some concrete answers and steps to take, as a Congress, to make all points of our drug development, sourcing, manufacture, and sale safer for consumers.

In the case of heparin, there are several points along this process where fingers can be pointed. But with ongoing investigations in China and an unclear timeline for getting real answers, we need to be able to move forward quickly and comprehensively to ensure that we are making our drug supply more secure and reliable. I hope that today we'll make progress toward that end.

Mr. Chairman, the confidence of American consumers has been shaken. The safety of their children's toys, the food they put on their table and the prescription drugs they take is questionable.

One of the reasons I'm so proud to be on this committee is that we can address those fears, and we are taking action to do just that. I know that Chairman Dingell has been hard at work on a large legislative package aimed at making our drugs, devices, food, and cosmetics safer. And I look forward to working with him and all my colleagues on the committee to pass as strong a bill as possible.

But it is also time for the administration to take some leadership. President Bush says he is committed to going to Beijing for the Olympics. I hope he also takes time to meet with Chinese officials to force action on their part to get them to give our inspectors the access they need to protect our consumers.

I look forward to hearing from our witnesses today. And again, I thank the family members for being here.

I yield back.

Mr. STUPAK. I thank the gentlewoman.

That concludes the opening statements by members of our subcommittee. I now call our first panel of witnesses.

On the first panel we have Mr. David Nelson, senior investigator for the Energy and Commerce Committee. Next, we have Ms. Colleen Hubley, who lost her husband, Randy, who was treated with recalled heparin. Next, we have Mr. Leroy Hubley, who lost his wife Bonnie, and son, Randy, who had been treated with recalled heparin. And we have Ms. Johanna Marie Staples, who lost her husband, Dennis, who had been treated with recalled heparin.

It's the policy of this subcommittee to take all testimony under oath. Please be advised that witnesses have the right, under the rules of the House, to be advised by counsel. Do any of you wish to be advised by counsel during your testimony?

Our witnesses indicated they did not. Therefore, I will administer the oath.

[Witnesses sworn.]

Let the record reflect the witnesses replied in the affirmative. Each witness is now under oath.

We will now hear from each witness a 5-minute opening statement. If you wish to submit a longer statement for the inclusion of the record, it will be done.

We will begin with opening statements. We'll begin with you, Mr. Nelson. If you would turn on the mic and pull it up there so we can hear you, you have 5 minutes for an opening statement.

STATEMENT OF DAVID NELSON, SENIOR INVESTIGATOR, COMMITTEE ON ENERGY AND COMMERCE, WASHINGTON, DC

Mr. NELSON. Good morning, Mr. Chairman, Mr. Shimkus and other members of the committee. I'm David Nelson, senior investigator on the staff. And I'm appearing here today to present the staff findings regarding the events that led to at least 81 deaths, and hundreds of severe allergic reactions associated with the manufacture of contaminated heparin, a blood thinner used widely in surgery and dialysis, whose active ingredient was produced in China.

The heparin case illustrates both the best and the worst of FDA's performance in drug crises. As with the melamine contamination of wheat gluten that resulted in an untold number of pet deaths last year, events which were highlighted by this subcommittee in hearings in July and October of 2007, FDA acted swiftly once the pattern of heparin's adverse events was identified.

FDA moved with speed and efficiency to identify the source of the adverse events, to remove the contaminated Baxter product from the market, to develop a methodology for identifying the contaminant, to require all existing inventories of finished product and active pharmaceutical ingredients to be tested to determine if they contain that contaminant, and to issue an import alert that required the testing of all heparin drug intermediates entering the country. At least we thought they did before we received Dr. Woodcock's testimony late yesterday, when we learned that the import alert covers only one source of Chinese heparin intermediates.

As their investigation progressed, FDA received reports from and provided information to, public health agencies around the world. This international coordination and collaboration with scientific experts domestically likely prevented many premature deaths and other adverse events that would have resulted from a lesser effort.

To date, FDA has assisted in identifying manufacturers in 11 countries as receiving contaminated heparin API from at least 12 Chinese sources. FDA's inspection of the Chinese factories, albeit after-the-fact, was done efficiently and professionally. After learning of the tainted heparin, FDA conducted a comprehensive inspection in February 2008 of Changzhou SPL, the Chinese source of the API to Baxter, and both of Changzhou SPL's immediate upstream suppliers of crude heparin to that plant. FDA inspectors issued a Form 483, noting significant deviations from current manufacturing practices.

Subsequently, FDA analyzed the company's response to the 483, issued an establishment inspection report, and ultimately a warning letter just last week, April 21, 2008, which detailed a host of serious deficiencies at the facility. That warning letter, issued the day before this subcommittee's hearing last week, effectively blocks imports from the Changzhou SPL facility until all outstanding issues regarding cGMPs have been resolved and the plant has been reinspected.

The staff investigation covered a number of serious shortcomings with FDA's operations and policies, as well as those of the manufacturers. I'll mention each briefly due to time constraints, but I'm prepared to elaborate on each if the committee have questions.

First, FDA has abandoned its mandatory pre-approval inspection policy. Had this policy been in place, the agency would have had no choice but to inspect the Changzhou plant in 2004 before permitting its products into the United States. Because it was optional, a clerical error allowed the official in charge of foreign inspections, a man who saw fit to resign just this past month, to dismiss the request for a pre-approval inspection because it mistakenly appeared in the computer system as having been inspected within the past 2 or 3 years—2 or 3 years before the 2004 request. I think it was inspected in 2002.

Second, FDA's woefully inadequate information technology systems resulted in the request to inspect the wrong plant. Now, that computer system permitted three correct unique identification numbers to be ignored. Instead, the official in charge of foreign inspections was permitted to focus only on the plant name that the chemist had entered as "Changzhou Pharmaceuticals" instead of "Changzhou SPL Pharmaceuticals."

Three, and most seriously, FDA's inspection policy fails to assess relative risk. Perhaps the most serious error made by the agency resulted from its failure to apply common sense to the foreign plant pre-approval inspection criteria. On the screens and on the chart resting there, the eight criteria, mandatory criteria for pre-approval inspections, are listed.

The plant mistakenly identified by CDER compliance had only been inspected for its ability to make two simple drugs, neither involving a biological extraction process like heparin. The misidentified plant was, A, located in China; B, the request involved inspection of an entirely new process for which the plant had never been inspected; and, C, the final product was ultimately used in a critical application—sterile injection in high-risk patients.

So FDA's pre-approval inspection policy, once it was no longer mandatory, revolved around criteria that ignored geography, ignored the complexity of the manufacturing process and ignored the sensitivity of the final product. It made no sense at all. None of these obvious criteria appeared in the guidance for pre-approval inspection, so FDA approved Baxter's application without sending anyone out to look at the plant. The role of corporate due diligence cannot be relied upon.

Wyatt, the predecessor owner of the heparin facility in New Jersey, did a validation process inspection of the Changzhou SPL plant in 2002. This was before the plant was operational. Baxter, who applied to import API from that plant in February of 2004, the sole customer for the production of the plant, did not even send an inspector over to Changzhou until 2007. That inspector apparently spent a day in the plant, found a few troubling items, accepted the SPL statement that it would be fixed, and pronounced the production process acceptable on February 26, 2008, the very day FDA would have been giving plant management an exit interview about its findings.

The cGMP violations found by FDA were so serious that we will not permit any product from the plant now into the United States until deficiencies noted in the warning letter have been corrected and the plant reinspected.

This is all the time I will take for the oral presentation. The full staff testimony has been presented for inclusion in the record. And I'll be glad to respond to any questions from the subcommittee. Thank you.

[The prepared statement of Mr. Nelson follows:]

STATEMENT OF DAVID NELSON

This is the fourth in a series of Subcommittee hearings concerning the Food and Drug Administration's (FDA) ability to adequately protect Americans from unsafe foreign manufactured pharmaceuticals. Today, the staff is prepared to summarize the results of its investigation of the events that led to at least 81 deaths and hundreds of severe allergic reactions associated with the manufacture of contaminated heparin, a blood thinner used widely in surgery and dialysis whose active ingredient was produced in China.

The heparin case illustrates both the best and the worst of FDA's performance under this Administration. As with the melamine contamination of wheat gluten that resulted in an untold number of pet deaths last year—events that were highlighted by this Subcommittee in hearings held in July and October of 2007,[1] FDA acted swiftly once the pattern of adverse events from heparin was identified.

FDA moved with speed and efficiency to carry out the following: identify the source of the adverse events; remove the contaminated Baxter product; develop a methodology for identifying the contaminant; require all existing inventories of finished product and active pharmaceutical ingredients (API) to be tested; and issue an Import Alert requiring the testing of heparin drug intermediates entering this country.

As their investigation progressed, FDA received reports from and provided information to public health agencies around the world. These aggressive actions that led to international coordination and the collaboration with scientific experts in this country likely prevented many premature deaths and further adverse events. To date, FDA has helped to identify manufacturers in 11 countries that received contaminated heparin from some 12 Chinese sources.

FDA's inspection of the Chinese factories, albeit after the fact, was also done efficiently and professionally. After learning of the tainted heparin, FDA conducted a comprehensive inspection in February 2008, of the Chinese source of API to Baxter, Changzhou SPL, and both of the upstream suppliers of crude heparin to that plant. FDA inspectors issued a Form 483 noting significant deviations from current Good Manufacturing Practices (cGMPs). Subsequently, FDA analyzed the company's response to the 483, issued an Establishment Inspection Report (EIR), and ultimately a Warning Letter on April 21, 2008, the day before this subcommittee's last hearing, which detailed a host of serious deficiencies at the facility.[2] The Warning Letter effectively blocks imports from Changzhou SPL until all outstanding issues regarding cGMPs have been resolved and the facility reinspected.

While FDA may respond quickly to a crisis when the danger to the public health is known, Committee staff found that its routinely poor performance as a regulatory agency, responsible for the safety of food, drugs, biologics, and medical devices, invites catastrophe and may have contributed to the tragic use of contaminated heparin on patients in the United States.

Our investigation uncovered a number of serious shortcomings with the operations and policies of FDA:[3]

1. FDA Has Abandoned Its Mandatory Pre-approval Inspection Policy

FDA acknowledges that they failed to inspect the Chinese facility, Changzhou SPL, prior to the approval of the Baxter supplemental application in 2004, which changed the source of the active pharmaceutical ingredient (API) for Baxter's heparin sodium products from the SPL Wisconsin plant to the newly constructed operation in China.

The Changzhou SPL facility is a joint venture by the U.S. firm Scientific Protein Laboratories (SPL), which also owns the heparin API plant in Wisconsin, and with Techpool, a Chinese firm that "consolidates" raw heparin from a number of workshops that extract crude heparin from the mucus linings of pig intestines. The SPL and Techpool facilities border one another in Changzhou.

---

[1] See, "Diminished Capacity: Can the FDA Assure the Safety and Security of the Nation's Food Supply?" Part II, Tuesday, July 17, 2007, and Part III, Thursday, October 11, 2007.

[2] Attached as Appendix A to this statement.

[3] The attached briefing memorandum for this hearing provides a timeline of the events from January 17, 2008, to date regarding the serious adverse events and deaths associated with the use of Baxter's heparin. FDA, Baxter, and Scientific Protein Laboratories (SPL) witnesses will provide further detail regarding these events.

While the Chinese Government disputes that counterfeit product was the cause of these adverse events, both FDA and the drug firms involved believe that to be the case. There is no dispute that raw material for the production of heparin sodium containing oversulfated, or hypersulfated, chondroitin sulfate was shipped to the U.S. market.

This form of chondroitin was apparently added to crude heparin in China at some stage in the production process by parties that have yet to be identified. This contaminant was not detected in the standard current United States Pharmacopoeia (USP) tests required of both the active pharmaceutical ingredient producer and the finished product manufacturer. Baxter and FDA have advised Committee staff that this counterfeit ingredient was most likely what caused the reported deaths and adverse health effects of patients receiving heparin.

Chondroitin sulfate is a very inexpensive product marketed as a dietary supplement here in the United States. The oversulfating process gives it anticoagulant properties that mimic heparin sodium, but at a much lower production cost. One FDA official stated that it costs approximately $20/kilogram (kg) to produce oversulfated chondroitin sulfate versus $2,000/kg to produce crude heparin. Accordingly, there is speculation that the contaminant was added deliberately to increase profits for the workshops and/or consolidators that ship the crude material to Changzhou SPL, SPL Wisconsin, and other heparin API producers.

While an inspection conducted in 2004 would not have detected the counterfeit ingredient in the crude heparin supply in 2007, it is possible that an FDA inspection at that time would have uncovered other indicators of potentially serious problems, including the failure of the SPL plant to register with Chinese authorities. Furthermore, an FDA inspection in 2004 might have revealed many of the serious deficiencies highlighted in FDA's inspection report of February 2008—a report that ultimately resulted in the issuance of the Warning Letter that effectively blocked exportation to the United States.

2. FDA's Woefully Inadequate Information Technology Systems Resulted in Identification of the Wrong Plant

For years, this Committee has highlighted deficiencies in FDA's various computer systems. As recently as last week, the Government Accountability Office (GAO) and the FDA Science Board testified before this Subcommittee that FDA computer systems are viewed as problematic at best and at worst, dangerous.[4] The heparin case illustrates the consequences of this problem.

FDA attributed the lack of pre-approval inspection of the Chinese SPL production facility to a clerical mistake by an FDA chemist who misidentified the plant in his request for such an inspection. The staff interviewed a number of individuals involved in the review process of the 2004 application filed by Baxter to change its API supplier from the Wisconsin source to the newly constructed plant in Changzhou, China. We found that an FDA employee did in fact choose the wrong plant from the pull down menu on his computer. He erroneously picked "Changzhou Pharmaceutical" instead of the correct name of the facility—"Changzhou SPL Pharmaceutical." Despite this error, he entered the correct "unique" New Drug Application (NDA) number and NDA supplement number for the Baxter application and the correct "unique" Drug Master File (DMF) number for the Changzhou SPL plant.

The FDA computer system, however, is not programmed to recognize these errors and alert the operator of the mistake. It accepted three unique numbers for one plant and permitted the selection of the incorrect plant from a menu of facilities for inspection. Furthermore, since FDA determines which facilities to inspect using the often confusing and nearly identical names of Chinese facilities, rather than the unique identifying numbers assigned to them, it was unlikely that this error would have been detected. Thus, the Center for Drug Evaluation and Research's (CDER) Office of Compliance processed the inspection request for the wrong Chinese facility.

3. FDA Inspection Policy Fails to Assess Relative Risks

Our investigation revealed that the wrongly identified facility, Changzhou Pharmaceutical, had been inspected in 2002, 2 years before the heparin request. That facility, however, has only been inspected for manufacturing two drugs: a simple, well-known, and well-characterized diuretic, hydrochlorothiazide, and a simple, semi-synthetic antibiotic, doxycycline. The manufacturing process for each of these drugs is very different from the extraction process required to produce crude heparin.

---

[4] See "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," Prepared for FDA Science Board, November 2007, page 5.

The FDA official who was in charge of determining which foreign plants must be inspected prior to approval to manufacture offered Committee staff two possible explanations for the error in his 2004 decision that Changzhou Pharmaceutical was "in compliance" and did not warrant an inspection. This official cited the relatively recent inspection conducted in 2002, and the misconception that the plant was a "crude heparin manufacturing facility," rather than one that manufactured the active pharmaceutical ingredient. Neither explanation justifies the decision to allow a new heparin intermediate supplier, with no history of producing complex, biological-based products, to export product to the United States without prior inspection of its manufacturing facilities.

Indeed, of the eight criteria employed by FDA during pre-approval inspections,[5] none involve geographic location, manufacturing complexity, or final product sensitivity. In fact, as far as Committee staff is aware, there is no systematic rationale for choosing which sites to inspect and which to ignore prior to approval by CDER of a foreign inspection application.

Intuitively, one would assume that among the most important criteria for prioritizing pre-approval inspections would be geography, complexity of the manufacturing process, and sensitivity of the final drug product. According to these common sense criteria, the supplemental request in 2004 from Baxter to change the manufacturing site of its heparin API from a plant in Wisconsin to one in Changzhou, China, should rank in the highest priority of risks. The plant is located in China, a country that FDA knows lacks a meaningful drug regulatory scheme and knows (or should have known) has manufacturers that to a large extent operate out-of-compliance. Such observations have been documented by FDA during inspections and observed by Committee staff during field investigations.

In addition, compared to most chemical syntheses, the process of extracting a drug from a biological source is a very different endeavor. While heparin sodium is an old drug, it is not a simple one to manufacture. Again, it would seem that FDA would prohibit any firm from providing to the U.S. market heparin sodium, its API, or crude heparin without first determining whether the firm could manufacture it properly. Manufacturing complexity should have triggered an inspection by FDA before the product was approved for export. Unfortunately, this was not the case.

In its final finished dosage form, heparin is a sterile drug administered to very sick patients, primarily those on dialysis for kidney failure and those undergoing open-heart surgery. Because patients who receive heparin are particularly vulnerable physically, the margin for error in production is virtually zero. Although the sensitivity of the final drug product should have guaranteed an FDA inspection, it did not because this is not a criterion for inspection.

4. The Role of Corporate Due Diligence Cannot Be Relied Upon

Committee staff investigation raised a number of questions about the due diligence performed by the various companies involved in this disaster. As previously mentioned, on April 21, 2008, FDA issued a warning letter to Changzhou SPL, where the adulterated heparin allegedly originated. In that letter, FDA details a litany of significant deviations from cGMPs discovered in the manufacture of heparin API at that plant. Those deviations were listed in summary form on FDA form 483 at the close of the team's initial inspection. According to the warning letter, the cGMP deviations observed by FDA at Changzhou SPL were sufficient to require its heparin API to be classified as adulterated under the Food, Drug, and Cosmetic Act.

According to FDA's inspection, the Changzhou SPL facility was unable to provide FDA with any assurance "that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities." FDA also found that the facility failed "to have adequate systems for evaluating the suppliers of crude heparin materials, or the crude materials themselves, to ensure that these materials are acceptable for use." Moreover, the methods employed to test heparin sodium United States Pharmacopoeia (USP) had not been verified to ensure suitability under actual conditions of use, and the equipment used to manufacture the product was "unsuitable" for its intended use.

In layman's terms, FDA determined that this plant was unable to manufacture drug product consistent with the requirements under the Food, Drug, and Cosmetic Act. An obvious question that must be asked in relation to FDA's inspection findings is why Baxter obtained drug product from a facility that FDA found to be unsuitable? More specifically, what due diligence did Baxter perform to determine that it could safely manufacture heparin API for the U.S. market before using this facility?

Committee staff found several facts that should have alerted Baxter to potential problems, but which appear to have been ignored. For example, Baxter's own records indicate that they were aware that the plant had never been inspected by

---

[5] Food and Drug Administration Compliance Program Guidance Manual 7346.832, pp. 10-11.

FDA. It seems very odd that Baxter accepted the risks of using this facility to obtain the API used to manufacture a sterile biologic without an FDA inspection. Moreover, this plant was apparently not one that China's State Food and Drug Administration was aware of since Chinese authorities listed it as a chemical plant rather than a licensed pharmaceutical plant. This too should have been cause for enhanced attention to its manufacturing processes.

Finally, Committee staff questions the quality and nature of the inspection performed by Baxter on September 20, 2007, relating to the factory's condition to manufacture drugs. According to records provided by Baxter to the Subcommittee, the scope of that audit was "to ascertain the cGMP compliance status of Changzhou SPL Co. LTD. facility in China for cGMP Active Pharmaceutical Ingredient manufacturing as well as other potential future products." The audit "consisted of an indepth review of Changzhou's quality systems and capabilities" and included documentation and procedures related to incoming materials, sampling procedures, stability operations, quality assurance processes, and stability operations. The results of Baxter's audit differ significantly from those reported by FDA, which inspected the facility only five months later.

The Baxter audit team satisfactorily closed out any problems they uncovered during their inspection in a February 26, 2008, letter to Baxter. This was done within days of the onsite inspection by FDA's own investigators, whose findings ultimately led to halting all imports from that facility. The radically different conclusions drawn from the inspections by Baxter and FDA, despite their close juxtaposition in time, suggest that either Baxter's auditors were less than competent or the facility fell radically out-of-compliance in the few months that elapsed between the two inspections.

This case also raises troubling questions when viewed in the context of recent testimony by FDA Commissioner Von Eschenbach extolling greater reliance on third party or self-inspection as a substitute for FDA performing its mission.

Moreover, this case demonstrates the quality and value of an FDA inspection. Despite the time and translation constraints inherent in an inspection in China, a team of professional FDA inspectors readily determined that Changzhou SPL could not supply safe API for the U.S. market-a conclusion that neither the Chinese authorities nor the corporations involved were willing or able to determine before hundreds of patients were seriously hurt or killed. Although it is most regrettable that FDA did not inspect this plant sooner, when it finally acted, FDA lived up to what is expected from such an important government agency-ensuring that our citizens are protected from unsafe pharmaceutical products.

Mr. STUPAK. Thank you, Mr. Nelson.

Ms. Hubley, for an opening statement, please.

STATEMENT OF COLLEEN HUBLEY, TOLEDO, OHIO

Ms. COLLEEN HUBLEY. I would like to thank you for allowing me to speak on behalf of my husband, Randy Hubley.

I am very familiar with heparin, not only because my husband was on dialysis for the last 18 months, but I have been a dialysis nurse for 7 years. Heparin is a lifeline for dialysis patients. It keeps the blood from sticking to the blood circuit while the dialyzer clears the blood.

As a dialysis nurse, I understand the importance of this drug. Now, because of the loss of my husband, I understand even more the importance of making sure that all drugs are safe.

Randy was a beloved father, stepfather, grandfather, son, brother, uncle, and last but not least, my soulmate. As his wife and an RN, I cared for him in every way possible. We were certain that no matter what came our way that we could handle it together. After all, I had been a nurse for 25 years, most as an open-heart intensive care nurse. Despite our hope, this man died on January 15th at 2:00 a.m. while I did CPR over him, powerless to save him.

He had started dialysis in May of 2006 when his kidney transplant rejected. After undergoing a surgery at the Cleveland Clinic, he needed to start in-center dialysis. On January 7, 2008, Randy started dialysis at the same clinic as his mother. This was the last week of his life.

I wish that I could tell you that the last few days of his life were good. It may give me some solace. However, the weekend prior to his death was awful. When he arrived home from dialysis on Friday, January 11th, he had low blood pressure, severe diarrhea, abdominal pain, jaw pain. His throat was sore and felt tight, making him feel he needed to use his inhaler to breathe. He could barely make it to the restroom. This was not my husband. He laid on the couch the whole weekend, trying to give a smile when he could.

Monday morning, he was too embarrassed to go to dialysis, fearful of having 12 other patients see him have an accident in a chair because it isn't a quick process to return the blood. He was too stubborn and disgusted with the thought of going to the emergency room and having another, "Well, really not sure what's going on here," answer. We settled on the couch to go to sleep so that I could be near him, and he promised that he would go if it didn't subside by the morning.

But at 2:00 a.m., I awoke to him clutching his abdomen, unable to breathe, and finally grabbing his chest. We had already called 911 before he collapsed. In what seemed like hours, I gave him CPR, with my son helping. Even when the paramedics arrived, they could barely get a breathing tube in his throat due to the swelling.

He was taken to the emergency room, and we were notified that, even if they got him back, it was hopeless. I watched my husband and my best friend slip away before my eyes.

As a nurse, I thought that I would be there to save my husband from any errors, but I guess I was naive. I never thought the lifesaving medication we were relying on might be contaminated.

Now, after learning that my husband was given contaminated heparin, I understand even more that everything in health care is vital. There should be no acceptable losses. If citizens are truly going to ever feel safe in this country going to the hospital, a doctor, taking your daily medication, we have a responsibility to make sure that everything that is given is free from contamination.

I understand that the FDA is overworked and understaffed. I deal with this every day as a nurse. But if you take a deep breath and think for one moment, "What if that was my mother or my husband?"

My husband was a fighter until the bitter end. He would have given anything for one more day. And I know that he would want me to make sure that this doesn't ever happen to anyone else. Please do not let his death be in vain. We, as a family, need to know that some good can come of this tragedy.

While the FDA and Baxter have failed to perform their duty to provide Americans with safe drugs, there are many Americans who have worked very hard to ensure a safe supply. An article was published last week in the New England Journal of Medicine connecting the symptoms of heparin patients, like my husband, to the contaminated drugs sold by Baxter. I want to thank those doctors and scientists who wrote that article and who have worked so hard to help unravel this puzzle and prove these Chinese imports were responsible.

I would like to thank this committee for shining light on these issues and, hopefully, for taking action to ensure that our drug supply is safe.

Thank you.

[The statement of Ms. Colleen Hubley follows:]

STATEMENT OF COLLEEN HUBLEY

I would like to thank you for allowing me to speak on behalf of my Husband, Randy Hubley. I am familiar with heparin not only because my husband was on dialysis for the last 18 months of his life, but also because I have been a dialysis nurse for 7 years.

heparin is a lifeline for dialysis patients. It keeps the blood from sticking to the blood circuit while the dialyser clears the blood. As a dialysis nurse, I understand the importance of this drug. Now, because of the loss of my husband, I understand even more the importance of making sure that all drugs are safe.

Randy was a beloved father, stepfather, grandfather, son, brother, uncle and last, but not least, my soulmate. As his wife and a RN, I cared for him in every way possible. We were certain that no matter what came our way, we would be able handle it together. after all, I had been in nursing for 25 years, most as an open-heart intensive care unit nurse. Despite our hope, this man died on January 15th at 2 am, while I did CPR over him in tears, powerless to save him.

Randy started dialysis in May of 2006, when his kidney transplant rejected. We were the first couple in the Toledo area to do “home hemodialysis.” This is a process that is done 6 days a week, 2½ hours at a time, in the comfort of our living room, as opposed to “in-center dialysis” done 3 days a week for 3–4 hours at a time. It was one way for us to gain a little more control over his care and also to increase his life expectancy. We were willing to do anything to keep him alive and well for as long as possible.

However, after undergoing a surgery at the Cleveland Clinic, Randy needed to start “in-center dialysis.” On January 7, 2008, Randy started dialysis at the same Toledo Fresenius clinic as his mother. This was the last week of his life. I wish I could tell you that at least the last few days of his life were good for Randy. I could take some solace in that. However, the weekend prior to his death was awful.

When he arrived home from dialysis on Friday, January 11, Randy had low blood pressure, severe diarrhea, abdominal pain, jaw pain, his throat was sore and felt “tight” to him, making him feel he needed his inhaler to breathe easier, something he didn’t normally need too often. Because of this, he barely could make it to the restroom. This was not my husband! He lay on the couch this whole weekend, trying to give me a smile when he could.

Monday morning he was too embarrassed to go to dialysis, fearful of having 12 other patients see him having diarrhea right in the chair, because it isn’t a quick process of returning the blood. He was too stubborn and disgusted with the thought of going to the ER and having another, “Well, were not really sure what’s going on” answer. We settled on the couch to sleep, so I could be near him. He promised that he would go if it didn’t subside by morning, but at 2 am I awoke to him clutching his abdomen, unable to breathe and finally grabbing his chest. We had already called 911 before he collapsed, and what seemed like hours I gave him CPR with my son helping me. Even when the paramedics arrived, they could barely get a breathing tube in his throat due to the swelling. He was taken to the ER and we were notified that even if they got him back, it was hopeless. I watched my husband and best friend slip away before my eyes.

There isn’t enough time to make anyone understand what a loss this has been. There is a void that can never be filled. Randy wanted to spend his last years fishing with his family and spending time with his loved ones. He will not get that chance now, and his grandson will never know what a beautiful person he was.

As a nurse, I thought I would be there to save my husband from any errors, but I guess I was naive. I never thought that the lifesaving medication we were relying on might be contaminated.

Now, after learning that my husband was given contaminated heparin, I understand even more that everything in healthcare is vital, that there should be no “acceptable losses.” If citizens are truly going to ever feel safe in this country, going to a hospital, doctor or taking our daily medication, we all have a responsibility to make sure that everything that is given is free from contamination. I understand that the FDA is overworked and understaffed, it is something I deal with everyday as a nurse, but if you take a deep breath and think for one moment, "What if that was my mother, my husband—what would I want done?"

My husband was a fighter until the bitter end. He would have given anything for one more day, and I know he would want me to make sure this doesn't ever happen to anyone else. Please do not let his death be in vain, We, as a family, need to know that some good can come of this tragedy.

While the FDA and Baxter have failed to perform their duty to provide Americans with safe drugs, there are many Americans who have worked very hard to ensure a safe supply.

An article was published last week in the New England Journal of Medicine connecting the symptoms of heparin patients like my husband to the contaminated drugs sold by Baxter. I want to thank those doctors and scientists who wrote that article and who have worked so hard to help unravel this puzzle and prove that these counterfeit Chinese imports were responsible.

And I want to thank this Committee for shining light on these issues and, hopefully, for taking action to insure that our drug supply is safe.

Respectfully Submitted,
Colleen Hubley
Toledo, Ohio

Mr. STUPAK. Thank you.

Mr. Hubley, sir? Do you want to pull that up and hit the button there, so the green light comes on? Thank you.

STATEMENT OF LEROY HUBLEY, TOLEDO, OHIO

Mr. LEROY HUBLEY. Well, I'm going to try to get through this.

Mr. STUPAK. Take your time.

Mr. LEROY HUBLEY. Mr. Chairman and members of the committee, thank you very much for inviting me to testify at today's important hearing.

My name is Leroy Hubley, and I'm from Toledo, Ohio. My wife, Bonnie, died in December after receiving heparin that was later recalled by Baxter. My son, Randy, died a month later under the same circumstances. And I hope that by telling their stories it will bring us to a closer answer that questions like families like mine desperately seek.

Bonnie was my wife for 48 years. She had a genetic disease known as polycystic kidneys. The disease affects the kidneys. Specifically, cysts grow in the kidneys. If too many cysts grow and they get too big, then the kidney becomes damaged. All my children have the same disease.

But in December 2007, she began to experience unusual circumstances during and after dialysis. She developed diarrhea, vomited, and felt like her heart was beating out of control while on dialysis. Then, during dialysis on December 17, 2007, she developed pain in her chest and abdomen, and the clinic had to call an ambulance.

Bonnie was rushed from the dialysis clinic to the hospital, Toledo Hospital. While at the hospital, she had a drop in blood pressure, difficulty breathing, severe diarrhea, and rapidly declined.

Three days later, on December 19, 2007, the doctors recommended we remove the breathing tube to end her suffering. Her entire family—our son, daughter-in-law, and grandchildren—were all there. Christmas music played in the background, and each one of us said our goodbyes. Then my wife and love of 48 years drifted away.

We did not realize at the time that the heparin she received may have been tainted. We simply tried to deal with the grief that follows the loss of a loved one. However, the nightmare returned only weeks later when my son, Randy, returned home to Toledo following surgery in Cleveland Clinic.

On January 7, 2007, he started dialysis at the same clinic in Toledo as my wife did. Randy had been receiving dialysis for approximately 8 months before at other locations. However, as you will hear my daughter-in-law Colleen describe—which you already did—when Randy started dialysis at the same clinic as my wife; he, too, developed nausea, low blood pressure, abdominal pain, fatigue, and diarrhea.

After a week later, my 47-year-old son was dead, leaving behind three children and a grandchild. Again, we attributed his death to a cruel twist of fate—that was, until we found out about the January recall of heparin. When we contacted the dialysis center, they confirmed our fears that the heparin given our loved ones had been recalled by Baxter. Now I am left to deal not only with the pain of losing my wife and son, but anger that an unsafe drug was permitted to be sold in this country.

The FDA and Baxter have not done their job. Somebody sure as hell didn't. I want to know what is going to be done to rectify this matter. I want to know if my daughter, Dawn, and the millions of others who continue to receive dialysis are safe.

I want to thank the scientists and doctors that have found a link between the counterfeit heparin and these deaths.

I hope the members of the committee will take steps to protect all of us and make it right.

Thank you very much.

[The prepared statement of Mr. Leroy Hubley follows:]

STATEMENT OF LEROY HUBLEY

Mr. Chairman and Members of the Committee:

Thank you very much for inviting me to testify at today's important hearing. My name is Leroy Hubley and I am from Toledo, Ohio.

My wife, Bonnie, died in December after receiving heparin that was later recalled by Baxter. My son, Randy, died a month later under similar circumstances. I hope that by telling their stories it will bring us all closer to answer the questions that families like mine desperately seek.

Bonnie was my wife of 48 years. She had a genetic disease known as polycystic kidney disease or "PKD." This disease affects the kidneys. Specifically, cysts grow in the kidneys. If too many cysts grow or if they get too big, the kidneys become damaged. All of my children also have this disorder.

Bonnie received a kidney transplant in 1995. Last year my wife's body started to reject her kidney. As a result, she had to start hemodialysis in October of 2007. At first, the dialysis sessions were uncomplicated.

But in December of 2007, she began to experience unusual symptoms during and after dialysis. She developed diarrhea, vomited, and felt like her heart was beating out of control while on dialysis. Then, during dialysis on December 17, 2008, she developed pain in her chest and abdomen and the clinic needed to call an ambulance.

Bonnie was rushed from the dialysis clinic to Toledo Hospital. While at the hospital she had a drop in blood pressure, difficulty breathing, severe diarrhea, and rapidly declined. Three days later on December 19, 2007, the doctors recommended removing her breathing tube to end her suffering. Her entire family—our son, daughters, in-laws, and grandchildren were all there. As Christmas music softly played in the background, we each said our goodbyes. Then my wife and love of 48 years drifted away.

We did not realize at that time that the heparin she received may have been tainted. We simply tried to deal with the grief that follows the loss of a loved one.

However, the nightmare returned only weeks later, when my son Randy, returned home to Toledo following a surgery at the Cleveland Clinic. On January 7, 2007, he started dialysis at the same Fresenius clinic in Toledo as Bonnie. Randy had been receiving hemodialysis for approximately eight months before at other locations. However, as you will hear my daughter in law Colleen Hubley describe, when Randy started dialysis at the Toledo Fresenius Clinic, he too developed nausea, low blood pressure, abdominal pain, fatigue, and diarrhea. About a week later, my 47-year-old son was dead, leaving behind his own three children and a grandchild.

Again, we attributed his death to a cruel twist of fate. That was, until we found out about the January recall of heparin. When we contacted the dialysis center, they confirmed our fear, that the heparin given to our loved ones had in fact been recalled by Baxter.

Now I am left to deal not only with the pain of losing my wife and son, but anger that an unsafe drug was permitted to be sold in this country. The FDA and Baxter have not done their job. I want to know what is going to be done to rectify the matter. I want to know if my daughter, Dawn, and the millions of others who continue to receive dialysis, are safe.

I want to thank the scientists and doctors who have found the link between the counterfeit heparin and these deaths. I hope that the members of this committee will take steps to protect us all and make it right.

Respectfully Submitted,
Leroy Hubley
Toledo, Ohio

Mr. STUPAK. Thank you for your testimony.

And, Ms. Staples, for your opening, if you would pull that forward and press the button there.

STATEMENT OF JOHANNA MARIE STAPLES, TOLEDO, OHIO

Ms. STAPLES. I want to sincerely thank the committee for providing the opportunity for us to share the stories of our loss. It's a remarkable thing you're doing, and it's appreciated beyond words.

In this land of freedom and opportunity, we've come to expect to be protected and safe. It's overwhelming to discover that there are circumstances beyond our control from which you are not sheltered. We have a false, empty sense of security, and we are neither safe from harm nor catastrophe.

Dennis Staples was important—important to me as my husband of nearly 32 years. He was my best friend, my confidant, my sounding board, companion, partner, editor, and financial advisor. He was my pride, my past, my present, my life, and my heart. He was important as a father, a new grandfather, a brother, uncle, brother-in-law too.

He was important to friends, family, acquaintances, and to his public. He was an entertainer and well-known radio announcer in Toledo for over 20 years. He was important to the region in which he lived. And, much to his dismay, he was an icon in the community that he so loved.

Without contempt or malice, he accepted the hand that life dealt him regarding his health. He accepted disease without anger and was resolved to do the best he could with whatever came his way.

On the last conscious day of my husband's life, he had a truly splendid morning. In a superb mood, he was looking forward to a special dinner out at a local steakhouse with dear friends. Dennis was thinking about last-minute preparations for his first-ever birthday party. He was astounded that he would actually be able to celebrate his 60th.

Upon awakening the last day, my husband carefully proposed his game plan for the day before I left to teach. Dennis went to dialysis the last day he knew life. Treatment was delayed because his permanent catheter was not functioning.

He needed dialysis, and his blood wouldn't flow. In an attempt to improve this problem, his nurse give him Activase. The procedure was deemed successful, he was given a bolus of heparin, and treatment resumed.

Shortly after he began dialysis this time, he suffered an event. He became unresponsive and stopped breathing, causing cardiac arrest. His caregiver was speaking to him at the time of the event, and CPR was immediately administered. Medical procedure was followed, 911 called, and paramedics arrived on the scene in just 3 minutes. Emergency personnel began life-saving measures, and I too arrived in moments.

We were transported by ambulance less than 5 minutes away to the hospital emergency room where ER staff was waiting. Again, Dennis received immediate attention.

My husband arrested and survived the event, but without neurological recovery. Professionals were unable to save his life, and he never again regained consciousness in spite of everyone's best efforts, continuous care, and speedy initiation of medical treatment.

I truly want this statement to be that very poignant and touching piece that exemplifies the man of whom I speak. I want to honestly reveal all the reasons why we are so devastated by his loss. I know I have the passion and the motivation, but I fear I don't have adequate skills to speak eloquently enough to give you a real description of the complex man I can no longer see, hear, touch or smell.

I loved my husband with all my heart and dearly miss him every minute of every day with an ache that cannot be dulled or cured. If he were taken to us even a day too soon, that day was still priceless to us, and we will never get it back.

Dennis lapsed into coma that day before he turned—the day he turned 60 years old. We lost Dennis, but he lost too. He lost his life, his birthday, his party, and the chance to visit one last time with all of his friends and loved ones nestled around him to celebrate his life with him.

Baxter supplied tainted heparin to medical facilities for use in patients in great need. Researchers have found the link between corrupted heparin and the deaths of many unsuspecting people. This drug certainly increased heparin's—Baxter's corporate bottom line. Baxter delivered larger dividends to stockholders according to their 2007 annual report. Board members received additional benefits while failing to recall a bad drug, a drug that was already known to have serious adverse effects.

So my husband and many other ailing patients who received that drug suffered needlessly. Dennis and many others died. Thank you.

[The prepared statement of Ms. Staples follows:]

STATEMENT OF JOHANNA STAPLES

I want to sincerely thank this committee for providing us this opportunity to speak and share the stories of our loss. It is a remarkable thing that you are doing for our families and we appreciate it beyond words. In this land of freedom we have come to expect that we are protected and safe. It is an overwhelming experience for us to find out that there are circumstances that are beyond our control—circumstances from which we are not safe. We might think we are protected from harm and catastrophe, but it is an empty and false sense of security. End-stage renal patients must be connected to a machine and submit to recurrent dialysis treatments. Each treatment lasts 4 or more hours while the patient's blood is systematically removed from their body and toxins are carefully cleared from their blood as it flows through the dialysis machine and then returned. This process is repeated usually three times per week and more for patients like my husband. In this process many life-saving drugs are used due to renal failure, drugs that are essential to this treatment. Patients need to know the drugs that they must use are reliable and secure. That's what I thought. Patients can remain on dialysis for an unlimited period of time. Actually they can remain on dialysis for many years. Transplantation is the ideal decision for someone with this disease, but my husband always felt that someone else should have the kidney and opportunity and he discarded the idea of receiving a transplant.

I so want this statement to be that truly poignant and touching piece that really makes you think about the man of whom I speak. I want it to be a statement that honestly reveals all the reasons why we are all so devastated by the loss of Dennis Staples. I know I have the passion and the motivation to tell you of our loss but I fear I don't have adequate skills to speak eloquently and give you a true sense that really shares with you all of the facets of the complex man that I can no longer see, hear, touch, or smell. I loved my husband with all my heart and dearly miss him every minute of every day with an ache that cannot be dulled or cured. Even if he was taken from us a single day too soon that day was still priceless to us and we can never get it back. Dennis lapsed into coma the day before he was to turn 60 years old. We lost Dennis—but he lost us too. He lost his life, his birthday, his party and his chance to visit one last time with his loved ones and his friends nestled around him to celebrate with him.

Dennis Staples was important. He was important because he was my husband of nearly 32 years. He was my confidant, my sounding board, my companion, my partner, my editor, my business partner, my financial advisor, my pride, my past, my present, my life, and my heart. He was important as a father and new grandfather. He was important to his brothers, his nieces, nephews, and to his brothers and sisters-in-law. He was important to his friends, his family, his acquaintances, and his public. He was an entertainer and well-known radio announcer in Toledo for over 20 years. He had many listeners who have reported and continue to report that they miss him dearly. He was important in the community in which he lived but he was also important to his family. He, much to his dismay, was an icon in the community that he so loved. He accepted the hand that was dealt him regarding his health without contempt or malice. He accepted his disease without anger and was resolved to do the best he could with whatever came his way.

Dennis Staples was a man who possessed incredible integrity. He was a man who had an amazing intellect and an extensive vocabulary. He had a quick wit and an equally remarkable capacity for love. He loved everything about life: politics, music, trivia, learning, cooking, performing, acting, reading, and writing. He loved his family and friends and he loved life. He was a humble man who lived in a body that was old before its time. He had a heart of gold and would share whatever he had to help out someone in need. In conversations he gave you unconditional attention and had a way of making you feel like he couldn't wait to hear what you would say next.

On the last day of my husband's conscious life he had a truly splendid morning. He was in a superb mood, busy planning a special dinner at a favorite local steak house with one of our beloved doctors and his wife. Dennis was actively thinking about last-minute preparations for his first-ever birthday party and he was so amazed that he would actually be able to celebrate the 60th anniversary of his birth. When we awoke that last day, he carefully laid out his proposal of the ideal plans for the day so that we would have the same game plan before I left for work to teach my disabled kindergarten students.

As I left the house for work Dennis said, "You go to school, and I'll go to dialysis and when we both get home, you can get me bathed and change my dressings, and I will relax while you get ready." He was looking forward to dinner out so much that he barely spoke of anything that wasn't related to dinner, his birthday and his party. This dinner would be our chance to spend quality time with a truly caring doctor that we had really good reasons to trust. This is a physician for whom we hold the greatest respect and he is a man to whom we owe so many thanks for repeatedly going above and beyond the call of duty on our behalf.

On our medical journey there have been a multitude of doctors and we have had the distinct pleasure of being connected with some of the very best. This is important because disease takes a horrific toll on its victims. That toll is key to the sheer number of doctors that must be involved in the life of a diabetic. To begin, there are complications with digestion, heart, eyes, lungs, kidneys, other organs and limbs. There are Critical Care, Primary Care and Infectious Disease Physicians; Cardiologists, Endocrinologists, Nephrologists, Neurologists, Ophthalmologists, Radiologists, Urologists, plus Pulmonary and Retina Specialists, along with Cardiac, General, Neuro-surgeons and Vascular Surgeons, and a host of other medical personnel who I haven't the time to name.

When our daughter Lexi picked up Dennis for his dialysis treatment that Wednesday, he was almost giddy with plans for the day. He was chatty and quick to share with her what he planned to do that evening. When they arrived at the treatment center, while Lexi was collecting and helping him into his wheelchair, they were approached by a firefighter who asked, "Do you need help?" My husband responded with a short and sweet answer, "No, thanks." Followed by, "Well good, because I would hate to see my hero fall down." The firefighter went on to talk to Dennis about how he had had a genuine impact upon his life when the young fireman-to-be was an intern at the radio station where my husband had worked with his partner, Bob Kelly. This young community helper praised Dennis again and offered him further assistance if he were ever to need it.

In the weeks leading up to his death, Dennis was made to suffer many indignities without complaint. He was no stranger to dreadful experiences. He worked hard to maintain his health and yet he still had to deal with losing his ability to walk and drive. This formerly independent man was forced to rely on the assistance of others to move about and to care for all of his personal needs. He needed others to help bathe and clothe him. He needed us to do his dressing changes. He needed assistance with every facet of his daily life—assistance for just about everything he did, for transportation, mobility, and for all his ongoing treatments.

Dennis would have worked far longer if his health hadn't interfered with his life plans. Twenty-eight months before he died, Dennis had to go on dialysis because his kidneys failed. Sixteen months before he died, he retired from his job because he could no longer reliably go to work. Yet, he was able to rebound and move on from all these things. But he could not survive the contaminated heparin.

There were many people who paid their respects at the funeral home. There were many people that I had never met. There were people who he helped when he worked as a counselor at a local hospital. There were people who listened to his daily radio program and missed hearing his voice. There were local politicians and well-known entertainers, local celebrities, and personalities from all types of media. We even received proclamations from both our mayor and the city council on my husband's behalf. In our local newspaper his passing was actually given celebrity obituary status. As my husband often marveled, he really felt that he had become a big fish in our little local pond. He would have been so touched to see the outpouring of grief from our community at his death—and that death was far too soon. Over the years, Dennis had made a multitude of local commercials for both radio and television and accordingly I am often reluctant to watch and/or listen to local stations for fear that I might be surprised and startled to hear his voice when I least expect it.

The last day of Dennis' conscious life he went to dialysis as usual. Treatment was delayed because his permanent catheter was not functioning and blood could not be pulled from nor returned to his body. He needed his dialysis. His nurse gave him a drug called Activase in an attempt to help his blood flow. This procedure was deemed successful so he was given a bolus of heparin and his treatment resumed. Shortly after Dennis began dialysis for the second time, he suffered an event. My husband became unresponsive and he stopped breathing causing cardiac arrest. His caregiver was speaking to him at the time of the event and CPR was immediately administered. Medical procedure was followed and 911 called, with paramedics arriving in only 3 minutes, since their station was located across the street and visible from the front of the center. Emergency personnel began life-saving measures. I arrived at the dialysis center in time to be transported by ambulance along with my husband in record time, to the hospital emergency room. This hospital was less than 5 minutes away from the treatment center where he arrested. Upon arrival at the emergency room, Dennis received immediate attention by a waiting ER staff. Dennis survived the event but without neurological recovery. He never again regained consciousness in spite of everyone's efforts, and the speedy initiation of medical treatment. Professionals were unable to save his life.

I worked hard to celebrate my husband's life and make my peace with his loss. I thought I was well on my way to learning how to deal with his passing—and then

I found out about the contaminated heparin. As people were permitted to suffer and die from this crop of tainted drugs, in 2007 Baxter Pharmaceuticals CEO Robert L. Parkinson, Jr., was paid, in total compensation, $17.6 million dollars, nearly 1.5 million dollars a month.

Baxter's global net sales totaled 11.3 billion in 2007, at an increase of 9% from 2006. Sales in the United States alone totaled over $4.8 billion, an increase of 5% over the prior year. International sales totaled over $6.4 billion, increasing 11% compared to the prior year. Baxter reinstituted quarterly scheduled payments of dividends in 2007, and increased the annual 2007 dividend rate by 15 percent. Heparin, a drug that could have been recalled sooner, made untold profits. It was made more economically with ingredients that could be produced less expensively in China. Baxter paid an increase of $340 million in cash dividends to shareholders and total dividends for 2007 were over $700 million.

In late 2007, Baxter's board of directors reevaluated stockholder dividends based on company profitability and they declared a quarterly dividend that represented a 30% increase over the previous quarterly rate. Company profitability surely increased for 2007—but at what cost? Baxter supplied tainted heparin for use in medical facilities to patients who were in need. This drug surely helped to increase Baxter's corporate bottom line. Baxter provided greater dividends to stockholders plus additional benefits to board members, while the corporation failed to recall a bad drug; a drug that was already known to have adverse effects—so my husband and many other ailing patients who received the drug suffered needlessly. Dennis and others died.

I just don't blame Baxter and their drive for profits. I also blame the FDA for not doing its job to ensure that the drugs sold in this country are safe.

In conclusion, I want to thank the hard working doctors and scientists who have worked to unravel this tale of deception. While Baxter and the FDA failed, the scientists and doctors who recently published their findings in the New England Journal of Medicine have done their job, and done it well. They have proven that the sudden drops in blood pressure and the other symptoms which my husband and others suffered from before their death were caused by the contamination.

Finally I want to thank this Committee, in advance, for doing its job and passing the laws that are needed to secure a safe drug supply for my fellow citizens.

Respectfully Submitted,
Johanna Staples
Toledo, Ohio

Mr. STUPAK. Thank you. And thank you to all of our witnesses on this panel and thanks for your courage and your eloquence in helping us out.

As I indicated in my opening statement, this is a series of hearings we have had. This is our sixth one on drug safety alone. And you certainly help to motivate us to work harder on this issue. You also put a human face on all these hearings that we have had.

I think this is the first one on drug safety where we actually had some victims come in, because it is difficult for you, just as it is for all of us up here to see these repeated mistakes, and hopefully you will motivate us to correct them with legislation and other things that we can do.

Let me, if I may, ask a few questions.

Ms. Hubley, you have confirmed that your husband was given heparin that was produced by Baxter. Is that correct?

Ms. COLLEEN HUBLEY. Yes.

Mr. STUPAK. You stated that your husband had been on dialysis since May of 2006?

Ms. COLLEEN HUBLEY. That is correct.

Mr. STUPAK. Had he ever previously suffered any adverse reactions to heparin?

Ms. COLLEEN HUBLEY. No, not that I was aware. And I did dialysis at home for him.

Mr. STUPAK. You stated you have been a nurse in the dialysis unit.

Ms. COLLEEN HUBLEY. Correct.

Mr. STUPAK. You also said you gave dialysis to your husband at home. Have any of your other patients had allergic reactions while they have been on heparin?

Ms. COLLEEN HUBLEY. You know, I knew that this question would probably come up; and it is very difficult to know.

When you are at work, you have 12 patients, sometimes more. Each one of them is getting a bolus of heparin and hourly heparin doses. I don't—I can't tell you for sure it was the heparin. We certainly weren't thinking that back in those months.

The side effects, did we see them? Yes. Some of them are normally seen in dialysis patients; some of them are not.

Were there more? If you ask my opinion, yes, I believe that there were.

Mr. STUPAK. OK. Thank you.

Mr. Hubley, if I may ask you a question or two. You stated your wife began dialysis in October of 2007 and that the first—at first, the dialysis sessions were uncomplicated.

Mr. LEROY HUBLEY. She started dialysis at the Toledo Hospital.

Mr. STUPAK. And that was in October of 2007?

Mr. LEROY HUBLEY. When she lost her kidney, the transplant she had for 12 years. And she was doing fine in the hospital. She didn't mind it a bit. I said, by God, maybe we won't have to need another transplant if you like dialysis.

She started going over to the one closest to the house. She only did about five or six times there. First time, I went over to pick her up, and the dialysis nurse said, you will have to come back in about an hour. She has a very high temperature.

The lawyer said, this is awful confusing.

But I went to pick her up an hour later. They told me, you'd better take her over to the emergency room because we can't get the temperature down. So we went over to the emergency room at Toledo Hospital, and she died right there in the waiting room.

They said, it's a damn good thing that she was here because you have 5 minutes to bring her back. They brought her back.

Prior to that, she was in the hospital for about 2 months because they didn't know what was wrong with her. She was losing her kidney, and they finally found out she was losing her kidney. Gave her all these tests. She was fine.

Then, after she died in the emergency room, they put her back in the hospital and says, Oh, well, she needs a bypass surgery. For crying out loud, you tested her for 2 months before and you didn't find anything wrong with her except she was losing her kidney. Whether she needed that or not, I don't know.

Then we put her in rehab. Then they shuttled her back and forth to the forensic center, the same place where she was at before. And a couple days later they called an ambulance, sent her back to Toledo Hospital, and she died a couple days later.

Mr. STUPAK. Let me ask you the same question I asked Colleen. Has it been confirmed that your wife had heparin manufactured by Baxter?

Mr. LEROY HUBLEY. Colleen found out from the dialysis center that they did have it. And they pulled it off the shelves right away.

Mr. STUPAK. Thank you.

Ms. Staples, you stated that your husband had been on dialysis for about 2 years, just over 2 years before his death?

Ms. STAPLES. Yes.

Mr. STUPAK. At any time prior had he suffered any adverse reactions to heparin?

Ms. STAPLES. Not to my knowledge, no.

Mr. STUPAK. Have you been able to confirm that your husband was given heparin produced by Baxter?

Ms. STAPLES. It was information that was requested and confirmed.

Mr. STUPAK. OK. Thank you.

Mr. Nelson, you indicated in your statement that there's an import alert for heparin, or the API, heparin API, active pharmaceutical ingredients, from Changzhou SPL only?

Mr. NELSON. That's right. We understood the import alert would cover all heparin intermediates coming in from China.

According to Dr. Woodcock's testimony, it only applied to Changzhou SPL.

Mr. STUPAK. OK. Were there other plants or companies in China that produced heparin?

Mr. NELSON. Well, the FDA has told us and the world that there's 12 Chinese sources, different Chinese sources of contaminated heparin, that have been confirmed.

Mr. STUPAK. OK. In the United States, the import alert is out for Changzhou heparin, correct?

Mr. NELSON. Changzhou heparin.

Mr. STUPAK. OK. How many ports can they ship into the United States? Is it like around 300?

Mr. NELSON. 321, I think.

Mr. STUPAK. 321. How many FDA inspectors do we have? Do you know?

Mr. NELSON. How many ports have FDA inspectors?

Ms. STAPLES. Yes.

Mr. NELSON. I believe about 90.

Mr. STUPAK. OK.

Mr. NELSON. That's not necessarily full-time, 24 hours a day.

Mr. STUPAK. So if you have approximately 300 ports where heparin can come in, possible, and only 90 inspectors or 100 inspectors at most, so our chance of catching it if it came in from different ports is 1 in 30—1 in 3?

Mr. NELSON. Well, it's certainly problematic.

We were out in San Francisco on a food investigation, and we watched the data entry reviewers, who are inspectors assigned to examine the electronic information coming in from Customs. And they had about 1,000 entries a day each or about 1 every 30 seconds where they had to make a decision as to what it was and whether it should be inspected.

Ms. STAPLES. OK. So human error could occur again, and heparin could come in if you have about 30 seconds to make a decision whether or not to allow this product into the United States?

Mr. NELSON. Well, it certainly does increase the chance of human error if there's no import alert.

Mr. STUPAK. Let me ask you this, Mr. Nelson: as the senior investigator, has the Committee received all the documents and conducted all the interviews that this committee felt necessary regarding the preapproval inspection process at the FDA on this heparin issue?

Mr. NELSON. No. We have been denied documents, and—to the best of my knowledge, we've been denied documents. They've supplied us a lot of documents. We haven't been able to locate any of them. They come from the Office of Chief Counsel, and we've been refused the opportunity to interview employees at the Office of Chief Counsel.

Mr. STUPAK. All right.

As a senior investigator, why is it necessary to receive the documents and to do the interviews that you wish to do from the FDA personnel or its lawyers?

Mr. NELSON. Well, the—we believe that the lawyers in the Office of Chief Counsel review all important policy decisions, must pass on all important policy decisions and many of the critical enforcement decisions, including warning letters and import alerts, before they're permitted to go into effect by the Agency.

Mr. STUPAK. OK. Mr. Nelson, Baxter appeared to have performed its own audit of the plant in September of 2007—that's at Changzhou SPL—and found that the plant was in compliance with good manufacturing practices. Is that true?

Mr. NELSON. That's correct. They sent somebody over there for 1 day.

Mr. STUPAK. OK. That was September of 2007; and 5 months later, after this heparin outbreak, the FDA found significant problems at this plant, and it wasn't in compliance with the good manufacturing practices. Is that correct?

Mr. NELSON. That's correct. In fact, it was so out of compliance that the conditions on the import alert are that it—it cannot be allowed to ship into the United States until not only have they responded to the criticisms that were found on the 483, but that FDA has to go over there and reinspect, which is something that rarely occurs.

Mr. STUPAK. Now, Mr. Nelson, there's a document book right there to your left. Under Exhibit No. 30 in the exhibit book, there appears to be a copy of the audit performed by Baxter, which is dated September 20, 2007.

Do you have that document, sir?

Mr. NELSON. I do, sir.

Mr. STUPAK. On the third page of the exhibit under section Audit Purpose, it states, and if I can quote, "To perform a GMP audit of the Changzhou SPL Company, Ltd., facility in China in order to verify the effectiveness of their quality systems and technical capabilities with regard to applicable Baxter and regulatory requirements."

Do you see that, sir?

Mr. NELSON. I do.

Mr. STUPAK. And is that the purpose of this audit?

Mr. NELSON. That's the stated purpose of the audit.

Mr. STUPAK. All right, Mr. Nelson.

Now, under the heading, Audit Scope, does it say the following—again, I quote—"To ascertain the cGMP compliance status of Changzhou SPL, the audit consisted of an in-depth review of Changzhou's quality systems and capabilities including but not limited to the documentation and procedures associated with the following areas."

Do you see that?

Mr. NELSON. I do. Yes, sir.

Mr. STUPAK. OK.

Now, Mr. Nelson, it appears that the areas examined by this audit were the same areas and issues examined by the FDA team a couple months later in February 2008. Is that correct?

Mr. NELSON. Generally, that's correct, sir.

Mr. STUPAK. OK. These areas that were examined include incoming materials and sampling procedures, warehouse, manufacturing areas, packaging areas, stability operations, QC, laboratory operations, and even the quality assurance process.

This appears that Baxter was performing a good manufacturing audit. Is that correct?

Mr. NELSON. That's correct.

Mr. STUPAK. Mr. Nelson, under the executive summary on that Exhibit No. 30, it appears that Baxter audit found only one major observation related to the CG&P which involved microbial limits testing, and that if—and that the one problem was addressed; and this facility should be considered approved for routine manufacturing of heparin, according to that document. Is that correct?

Mr. NELSON. I believe so, sir.

Mr. STUPAK. Exhibit No. 30 also contains a letter dated September 18, 2007, from Baxter to Dr. Yan Wang, I'm sorry. Dr. Yan Wang. In this letter, Baxter notes and I quote, "The current audit risk assessment that you—your facility is rated as acceptable."

Do you see that? It's on the first page of Exhibit No. 30.

Mr. NELSON. On the first page?

Mr. STUPAK. Yes.

Mr. NELSON. Yes, sir.

Mr. STUPAK. OK. That's the December 18, 2000—so Baxter considered this facility acceptable in December of 2007, is that correct?

Mr. NELSON. That's correct.

Mr. STUPAK. All right. September of 2007. I'm sorry.

Let me go to Exhibit 31, next exhibit, and this is another letter to Dr. Yan Wang, dated February 26, 2008, in Exhibit 31, where Baxter notes that the few audit observations that apparently were observed, and it states, "have been satisfactorily addressed." is that correct?

Mr. NELSON. That's correct.

Mr. STUPAK. In fact, Baxter notes in this letter, quote, "We are pleased to inform you that this audit has been closed."

Do you see that?

Mr. NELSON. I do, sir.

Mr. STUPAK. Thank you.

Mr. Shimkus for questions, please.

Mr. SHIMKUS. Thank you, Mr. Chairman. Again, we appreciate your testimony. And we're sorry that you have to be here with those results.

I think many Members of Congress—there's a piece of legislation, the Kidney Care Improvement Act—something to that extent—which has driven a lot of Members to visit dialysis centers in the past 2 years. I think I've attended and visited five separate ones throughout my congressional district. So there are amazing things we can do when you are assured of quality. I appreciate your service in that. I met one guy who came out here who was on dialysis for 25 years, which is amazing.

My questions are going to be brief to the grieving family members: all three of you learned of the heparin recall after the deaths. Is that correct?

Ms. COLLEEN HUBLEY. Yes.

Mr. SHIMKUS. And how did you learn? How did you get that information?

Ms. COLLEEN HUBLEY. When I returned from my bereavement leave with my husband, I hadn't kept in contact with really anyone from work.

I came back, and there was notes posted all over. And my patients were actually asking me, is the heparin okay; is the heparin okay? You know, everyone wanted to run heparin-free, which is awful. You don't want to do that.

And I—I was like a little bit shell-shocked, I guess, and I responded to them, Yes, it's all right. They took it off the shelves. And we were using a dilute heparin at that time.

I sat down for a minute and read some of my e-mails. And obviously this is my job probably on the line right now, but I read it, and the things just kept playing into my head. And I'm thinking, it's a huge coincidence if the heparin didn't have something to do with it. The symptoms were very consistent with what I saw in my husband and in my mother-in-law.

Mr. SHIMKUS. Of course, Mr. Hubley, just from your daughter-in-law?

Mr. LEROY HUBLEY. Yes.

Mr. SHIMKUS. And Ms. Staples?

You will need the mic. I'm sorry.

Ms. STAPLES. I came in close contact with folks that had treated my husband and found out about the recall. And then I said, Wait, he had to have the same heparin.

Mr. SHIMKUS. Right.

Ms. STAPLES. How long was this in effect? How long was there a problem?

Mr. SHIMKUS. Right.

Ms. STAPLES. And——

Mr. SHIMKUS. Then the other thing, since a lot of us have visited these dialysis centers—I mean, there are multiple chairs, multiple facilities, people in the waiting room, people outside. And we know those who are on dialysis, they run the gamut of health. They're all in dialysis, but as far as the other healthy conditions, I imagine that lot number, as you mentioned, probably had a lot of your—patients concerned because—I mean, you imagine a lot, a big lot, would go to the same facility.

So a lot of these other patients that probably were healthier did not have the extreme adverse effects, but they probably still had some effects, would you——

Ms. COLLEEN HUBLEY. Right. And I think it did vary. In my opinion, I think you have—you do have the spectrum. Of all of you sitting up there, if you were all on the machine, you all have different co-morbidities that complicate your health.

Mr. SHIMKUS. Right.

Ms. COLLEEN HUBLEY. And the people who were sicker responded less favorably.

Mr. SHIMKUS. And as a former critical care nurse and—I mean, I had open heart surgery 3 years ago. So I understand all that work you've done in there. And when your life is on the line, you really appreciate the professionals who do that type of service.

Let me ask you, has there ever been any follow-up by the Centers for Disease Control or any other Federal agencies to you individually?

Ms. COLLEEN HUBLEY. No.

Mr. SHIMKUS. Mr. Hubley, same?

Mr. LEROY HUBLEY. No.

Mr. SHIMKUS. Ms. Staples?

Ms. STAPLES. No.

Mr. SHIMKUS. I think my follow-up from the chairman is, so you were never contacted by the CDC or anybody else?

Ms. COLLEEN HUBLEY. No.

Mr. SHIMKUS. Mr. Nelson, thank you for your work. It's new for me to have someone on staff right there so I can grill and ask questions to.

It is maintained by the FDA that the manufacturers—that a preapproval inspection would not have identified the contamination. For example, on page 9 of her testimony Dr. Woodcock states, there is no justification for the theory that contamination of heparin would have been prevented if the inspection of the Changzhou SPL had occurred in 2004.

Would you care to comment on that statement?

Mr. NELSON. Yes. But first, Mr. Shimkus, it has been a completely bipartisan investigation. The counsel sitting next to you could have been sitting down here in terms of his knowledge of the process.

Mr. SHIMKUS. We're very fortunate to have him.

And just for the folks in attendance, I'm new on this committee. But the staff, the bipartisan staff, works well on both sides. So I appreciate that comment.

Mr. NELSON. I think it's intuitively obvious that an inspection in 2004 is not going to catch contaminated heparin introduced, or contaminants introduced, into the manufacturing process in 2007. But that's not the right question.

Given the observations that were found by the FDA inspectors in February, the serious allegations of the deficiencies, particularly in the control of the supply chain by Changzhou SPL, would it ever have been allowed to ship product into the United States with that dicey a sourcing of ingredients itself? That's the real question.

Clearly, if the plant was in the same shape, the records were in the same shape—and we have no reason to believe they were in any better shape back in 2004—the plant would have not been allowed to ship the contaminated product into the United States. Baxter would have had to continue to source out of Wisconsin or somewhere else. And so there is some chance that an inspection in 2004 would have prevented this, yes, sir.

Mr. SHIMKUS. And that's kind of the comments that we were talking about in last week's hearing, about just reviewing the manufacturing processes may have helped—may help in this whole process.

The failure of the FDA to initially inspect has been attributed to the misidentification of the Chinese plant. Does FDA maintain that it would have inspected the plant if it weren't for the clerical error?

Mr. NELSON. The head of the Foreign Operations Division in the Center—CDER compliance, the person that made the decision in this particular case and would be making this decision if the same case would arise today, said that he—had he had the same information today that he had back then, he still wouldn't have sent out inspectors.

And the critical question here is, why does—why do CDER's policies that permit an option of an inspection to determine whether a plant coming online, or part of a plant coming online, is capable of producing the material, ignore the fact that the plant is in China? I mean, the FDA knows full well, from all the GMP inspections they do do in China, that it's really problematic whether there's going to be serious GMP problems at any of the plants they inspect there, because the Chinese don't have a decent inspection system, and they know it.

Secondly, they ignored the fact that while it was a misidentified plant, the plant they did identify had never manufactured heparin or any similar substance, ever. It had been inspected for hydrochlorothiazide manufacture, which is a simple diuretic, and it had been inspected for doxycycline, which is a relatively simple tetracycline-like antibiotic. But it had never produced a plant that came from—a substance that came from a biological extraction process like heparin.

And thirdly, there seems to be no accounting for the fact that this raw material was going to go into a process and come out as a drug that was sterile for critical use. I mean, one would think there would be special care taken for the raw ingredients that go into sterile products at the end use. And I'm sure that the individual involved was not aware of the possible contamination, wasn't aware that the USP tests wouldn't have detected it. But the fact of the matter is that there is some risk, and they should have sent somebody over there.

Mr. SHIMKUS. And thank you. And I will yield back my time.

Mr. STUPAK. I thank the gentleman.

Ms. Schakowsky for questions, please.

Ms. SCHAKOWSKY. First, let me express my gratitude to David Nelson for the great work that he and the investigative staff have done on this. I really appreciate it.

I wonder if the Committee—has the Committee gotten the documents and interviews that we requested regarding the preapproval inspection process at the FDA?

Mr. NELSON. We've gotten interviews of all the operational people that we requested to be interviewed. We have not gotten interviews with the counsel that make many of these decisions or at least have veto authority over these decisions.

Ms. SCHAKOWSKY. And why is it necessary to get documents and interviews from FDA lawyers?

Mr. NELSON. Because they have a very influential role in policy.

There's an expression that I've heard from more than one member of the Food and Drug bar that goes like this: If FDA wants to do something and we agree with it, it's a question of policy, and they can do it; if we disagree with it, it's a question of law, and it's our call. And that has been consistent through many administrations.

The Office of Chief Counsel exerts an enormous amount of influence over FDA policy and, in this particular case, over enforcement decisions.

Ms. SCHAKOWSKY. So you are saying that the—that they actually have veto power over any policy change?

Mr. NELSON. Generally, yes. I don't have 100 percent certainty of that, but that's certainly the events—the questions that we've looked into, that's been true.

Ms. SCHAKOWSKY. Would the lawyers also have a say in the issuance of import alerts?

Mr. NELSON. Yes.

Ms. SCHAKOWSKY. All of them? They sign off on them? Is that——

Mr. NELSON. At least all the broad ones they do, and also the warning letters.

Ms. SCHAKOWSKY. Has this constrained the Agency in taking action to protect the public from unsafe food and drugs?

Mr. NELSON. Yes. There seems to have been a shift in policy in recent years. And I don't mean to attribute it solely to this administration; there's a pendulum that swings back and forth.

But where we've been in the more deregulatory era of this administration, there have been interpretations coming out of the Office of General Counsel that have restricted—they have a very restrictive or conservative view of what FDA's authority is that is not consistent with precedence in earlier years. And as far as I know, it's not the result of court decisions, but rather a change in FDA's view—counsel's view of the law.

Ms. SCHAKOWSKY. Well, we were told after the deaths in Haiti and Panama from diethylene glycol that had been substituted or added to glycerin in China and cough syrup and other medications that CDER asked for an import alert that would require testing of all batches of glycerin from China. The Office of Chief Counsel said such an alert would exceed the legal authority of the Agency, but they cited no law to that effect.

Mr. NELSON. That's what we were told by FDA enforcement personnel.

Ms. SCHAKOWSKY. So the position of the chief counsel was that Americans had to die before importers would be required to test their glycerin from China?

Mr. NELSON. So it would appear.

I mean, the question is, can you show that there is an appearance that the product is violative? And apparently if it's violative elsewhere to the point of being fatal, it doesn't count.

Ms. SCHAKOWSKY. I think you answered this: is this consistent with the legal constraints passed on FDA in the past? You are saying that there seems to have been a change in policy in this regard?

Mr. NELSON. In recent years there's been an announced change in policy. I mean, the number of warning letters that were permitted under the first chief counsel in the current Bush administration greatly, greatly restricted the use of warning letters and, presumably, of import alerts.

Ms. SCHAKOWSKY. So what does this tell us about the need to enhance the ability of FDA to stop drugs and other imported products that threaten the public health?

Mr. NELSON. Well, I think it clearly shows that Congress, if it wants tighter enforcement, if it wants the FDA to be able to act to protect the public health more readily and easily, regardless of who happens to be the chief counsel at the time, that it needs to make that authority very explicit in law, so there's no—there's no ambiguity.

Ms. SCHAKOWSKY. So would you say then—since that apparent change then—in general, Americans are less safe when it comes to feeling secure when it comes to their prescription drugs?

Mr. NELSON. That's not just my opinion. That's the opinion of a lot of the operational field personnel inside FDA that we've talked to.

Ms. SCHAKOWSKY. Once again, as I did in my opening statement, let me thank the family members. You know, putting a human face on that, talking about your loved ones, as hard as it may be, adds an urgency to the issue. And I can assure you that this committee will do everything it can under the leadership of Mr. Stupak and Mr. Dingell to adequately respond to the pain that you're feeling.

Thank you.

Mr. STUPAK. I thank the gentlewoman.

Mr. Burgess for questions, please.

Mr. BURGESS. Thank you, Mr. Chairman.

Mr. Nelson, this hypersulfated chondroitin sulfate, where is it used? Does it have a legitimate use at some point?

Mr. NELSON. Well, there are plants in China that produce it. We have—we've seen Web sites where it's available for sale. There is a Chinese patent, that I believe is in the exhibit book——

Mr. BURGESS. Yes, 32 is under the tab.

Mr. NELSON [continuing]. That was translated and provided to us by counsel for SPL; and it prefers—actually, that patent refers to a U.S. patent that specifically addresses the question of—in fact, it argues that the—this oversulfated ingredient will actually enhance heparin's qualities, blood-thinning properties.

Mr. BURGESS. Now, is that held to be the case in China or is that the case in this country? Would anyone reasonably think that this would be a good idea?

Mr. NELSON. Well, nobody in this country could add that to a drug product without having filed an application with the Food and Drug Administration. I have no indication that that's happened.

Just because something's been patented doesn't necessarily mean it works, and it doesn't necessarily mean there aren't adverse consequences that may have been identified in test tubes that don't occur until it's put into human beings.

Mr. BURGESS. Well, I guess what I'm getting at, does this stuff show up anywhere in commerce in China? Is it found to be useful for any type of treatment?

Mr. NELSON. I don't know of its uses. But it is produced and sold.

Mr. BURGESS. Produced and sold. And in any sort of quantity?

Mr. NELSON. I can't answer that. There's Web sites that we've found, but I have no idea what it's sold for.

Mr. BURGESS. Would it be cheaper than the active ingredient in heparin?

Mr. NELSON. We've looked into that.

Chondroitin sulfate is a common dietary supplement in the United States, and it sells for somewhere between $20 and $60 a kilo in wholesale form. The oversulfating adds some cost to it. We haven't been able to get an exact number on that, but it's not a huge addition to the cost, we're told. And yet the—a kilo of heparin is $2,000. So it's somewhere approaching 100 times less expensive.

Mr. BURGESS. So for a person who didn't care what they were doing, there would be a financial incentive.

Mr. NELSON. Clearly. As there was in adding the melamine, as there is in adding—in substituting or adding the diethylene glycol to glycerin.

Mr. BURGESS. But this compound is so stealthy because of the fact that it hides in the normal USP testing under the peak for heparin, is that correct?

Mr. NELSON. That's what—that's what I'm told, yes.

Mr. BURGESS. So unless you do very sophisticated testing to break out that peak, you're not going to know if it's hiding in there; is that correct?

Mr. NELSON. Sophisticated and relatively expensive, although not on a per-dose basis. We asked specifically what the cost was for the testing. We're told $12,000 to $14,000 a lot, which comes out to about 1.7 cents a dose.

Mr. BURGESS. So certainly within the realm of possibility as far as the pricing.

So now, going forward, will we be doing that testing at every port of entry in this country?

Mr. NELSON. That's a question you need to direct to Dr. Woodcock, because what we're going to do going forward isn't obvious from what FDA has done today.

Mr. BURGESS. It would just seem to me, sitting here, to make sense. It's going to be very, very difficult to do inspections across China, India—wherever else we may need to do them. What is it, 3,000 or 6,000 foreign drug manufacturer applications that are on file with the FDA? It's a lot.

Mr. NELSON. It's a lot. It varies everytime you ask them.

Mr. BURGESS. And if you're going to do 20 percent—every 5 years or something, I think, was a figure that sticks in my mind; and don't quote me.

But I mean, that's a lot of inspections to do, and it just seems to me if—now that we've identified this as a potential problem, it's hard to imagine that people are going to be able to resist the financial temptation to perhaps try it again—maybe not next year, maybe not the year after, but a decade from now.

Would it not seem reasonable, rather than try to go everywhere, that we would have to go across the world to test that product as it comes into our country?

Mr. NELSON. It's a complicated question. I mean, the general principle that FDA operates under, that QAQC managers operate under, is, you can't test into compliance. You have to understand the entire process because——

Mr. BURGESS. If I could just interrupt you, this isn't testing into compliance. This is thuggery. This is thievery. This is high crime and a direct assault on the American public.

I mean, this is not just testing for normal product manufacture, in my opinion, for what it's worth. Someone did this deliberately. They found a product much cheaper than the active ingredient. We can hide it under the peak, under their normal testing, and no one will be the wiser until people drop dead, at which time we've made a lot of money. And we're off to doing other things.

But it's not something that we would normally encounter in the normal manufacture. There's no way to get hypersulfated chondroitin sulfate in the normal manufacture of porcine intestine heparin; is that correct?

Mr. NELSON. That's my understanding.

Mr. BURGESS. So someone with malice aforethought has to do something to get it into the chain of commerce; is that correct?

Mr. NELSON. That's correct.

Mr. BURGESS. Same with the melamine in the dog food.

Mr. NELSON. Yes. And the melamine provides an interesting analogy. And I don't know whether this really holds, but melamine in the dog food was so that the protein test would show greater protein than the wheat flour or wheat gluten itself.

That was an innovation occasioned by the fact that 10 years earlier they had developed another substance that did the same thing, but then tests were developed for that. So they had to find something else to fool the test.

Mr. BURGESS. Right.

Mr. NELSON. And I don't know enough about the chemistry of this drug or these compounds to know, but it seems to me that if we develop a test that identifies hypersulfated chondroitin sulfate and that's all we do, that somebody will find another way to beat that test.

Mr. BURGESS. But it's a superanalytical mass spec in microcapillary electrophoresis, if we're doing that to every heparin product at 1.7 cents a dose, I mean that's a pretty cheap insurance. I would imagine Baxter in the future would not want to market a product that didn't have at least that level of certainty around it.

But it sure begs the question—I mean, melamine, okay, that's a pretty crude effort; and if you're looking, you are going to be able to find it. But this was not crude. This was sophisticated. This was stealthy.

Melamine was a thumb on the scale; this is a knife in the back for someone that I think deliberately intended harm. To whom, I don't know—the United States pharmaceutical industry, patients, individual patients? I have no idea. But this is much more egregious than the finding of a high nitrogen inert product in dog food, in my opinion.

Ms. Hubley, let me just ask you, because you are the dialysis nurse and the expert about dialysis centers that is with us, and thank you for being with us. I know it's been difficult for you and your family.

You know, heparin's not a completely innocuous drug. I mean, when I prescribed it, it scared me to death, to be perfectly frank. And there are some side effects that can occur.

Did you have a procedure? Did the dialysis centers generally have a procedure for documenting side effects for any medication? Not just for heparin, but during the process of the dialysis, whether it be the dialysis bath itself or any of the medications that are used?

Ms. COLLEEN HUBLEY. Yes, we do.

Mr. BURGESS. And what typically happens to that list of adverse events, or side effects, however you might characterize them?

Ms. COLLEEN HUBLEY. They're filed with our compliance book folder that our clinic manager has.

Mr. BURGESS. And from time to time that's reviewed by whom?

Ms. COLLEEN HUBLEY. The clinic manager, regional manager, and, I'm assuming, probably the higher-ups.

Mr. BURGESS. Yes. I guess what I'm getting at, this data is being collected. We've gone through a lot in this committee about the information technology available to the FDA. At some point is that data de-identified and aggregated and submitted off to someone so that trends can be followed?

Ms. COLLEEN HUBLEY. You know, I don't—I think it's a very difficult trend to follow.

You have people come in, and some patients may get ill on dialysis without heparin; some may get sick with heparin. But there were things that—in the last several months, prior to all of that, that as you look back, you don't know how it happened.

Mr. BURGESS. And that's what I'm getting at. How is it that normal processes would identify this?

I have talked to veterinarians back in my district, to talk about pet deaths, before the melamine stuff came to light. And, of course, in a veterinary practice, you might accept the fact that no one was keeping track of the side effects from eating dog food.

But in a dialysis center where you have a relatively ill and restricted population, is there some way to feed that information back to whomever, be it the FDA or some other agency?

Ms. COLLEEN HUBLEY. Yes. Because if a patient has an untoward reaction or something that occurs during dialysis, it's noted in the charting. Now, it may not require a——

Mr. BURGESS. A notification?

Ms. COLLEEN HUBLEY. Yes. A form that we would have to fill out. But it would definitely be in the charting, because if you are treating a low blood pressure, you are charting what you are doing for that low blood pressure. If someone is having severe pain on treatment, you're going to chart that.

So, I mean, it would be difficult. But yes, it could be done.

Mr. BURGESS. OK. All right.

Thank you, Mr. Chairman. I will yield back the balance of my time.

Mr. STUPAK. I thank the gentleman.

For adverse events, as you are well aware, I think it's been about 6 years, FDA's been required to put 1-800-FDA-1088 to report adverse events.

It's been 6 years; they still haven't done it. So for people to report adverse events, if we're waiting for the FDA, it will be a cold day in you-know-where.

Mr. Melancon—not in your district. But Mr. Melancon for questions, please.

Mr. MELANCON. Let me thank the families for putting a face on this concern and this dilemma for the Congress and for the American public. And just because you are not getting all the questions doesn't mean that you haven't served a great purpose. And I thank you for that.

Mr. Nelson, is it possible—and just to do some follow-up to what the chairman was asking earlier—is it possible that Baxter appeared to perform an audit that found almost no major deviations from the cGMPs just 5 months prior to FDA's inspection and closed out this audit about the same time your inspection of Changzhou SPL was concluding, and yet your audit found so many problems with this plant that it barred its product from entering the United States?

What explains why your inspection found major problems while Baxter's audit found only a handful of minor deviations?

Mr. NELSON. Well, just to be clear, Mr. Melancon, we didn't do the GMP investigation. What we were reporting on is the results of the FDA's——

Mr. MELANCON. Yes, FDA. I'm sorry.

Mr. NELSON [continuing]. GMP investigations. And it is conceivably possible—well, no, it isn't. If you look carefully at the observations, it really isn't possible for a plant to have fallen that far out of compliance in 5 months.

The Baxter audit, cGMP audit in 2007, some 3 years after they began receiving product from the plant, was performed in a day. I have no idea, but I suspect that they didn't have—they had to rely entirely upon the company for translation of the records, and they obviously didn't look back very carefully at the supply chain. I mean, FDA at least went—not only inspected the plant but went back to the consolidators.

If we could put that slide up again, showing the supply chain in China, you can see that Changzhou SPL used two consolidators. These consolidators are putting together the crude heparin that is actually manufactured in the workshops. It's combining them. It's basically preparing for them to go into the Changzhou SPL plant. And the FDA went to the two consolidators that supplied Changzhou SPL.

One of the consolidators is Changzhou SPL's partner, the 45 percent partner; and, in fact, the Changzhou—Changzhou, I'm sorry, SPL plant joins the consolidators' operation in China, the tech pool operation in China.

Mr. MELANCON. Should the consolidators or should Changzhou SPL be the place for quality control? Or is it one and the same?

Mr. NELSON. It's got to be throughout the entire system, obviously.

Mr. MELANCON. Yes, from the beginning, right.

In your mind, was Baxter's audit insufficient, or did the plant just fall out of compliance? And does this suggest that Baxter's audit missed major problems that were occurring at this facility?

FDA's team was able with just two people in about a week to find so many problems with this plant; and we're now barring products from this facility from entering the United States.

I mean, why is it so easy when our guys went in?

Mr. NELSON. Well, I think that there's—there may have been a difference in the—there is certainly a time difference.

Mr. MELANCON. The time difference was 5 months.

Mr. NELSON. Well, no. There was a time difference in the amount of time spent in the plant. Baxter had one person go in there for 1 day. FDA—which for a plant of this complexity, I'm told, usually takes a couple of weeks if it was here in the United States—sent two inspectors, one, a chemist, to review the laboratory practices and one investigator to do the rest of the GMP investigation. And they had 5 days at the facility.

So if you want a measure of how hard people were looking, time alone would suggest a difference between what FDA was looking for and what Baxter was looking for, although they should have had the same concern about quality.

Mr. MELANCON. Just the time of travel to get to China, they could have done what they did, it appears, in that 1 day over the telephone.

We've been told repeatedly by the drug industry that they police their own facilities in the supply chains. What kind of grade would you give Baxter in how it policed this facility? And if, in fact, FDA was able to find the kinds of cGMP deviations, as noted in Ms. Brown's report, nearly 5 months after Baxter's inspection?

Mr. NELSON. Well, Baxter's was an incomplete, bordering on failure.

Mr. MELANCON. Did Baxter believe this plant was suitable in how it produced heparin API for the U.S. market, whereas the government agency responsible for protecting the public health, said this plant was unsuitable once it conducted its own investigation? So is that the case?

Mr. NELSON. It would appear to be the case. We have both the FDA and the company here today, and I suggest that those questions could be put to them.

But the appearance is clearly—you are clearly correct.

Mr. MELANCON. Thank you, Mr. Nelson.

And I yield back my time.

Mr. STUPAK. I thank the gentleman.

Mr. Inslee for questions, please. Both Mr. Inslee and Mr. Melancon, if you have opening statements, we'll put them in the record if you so wish.

Mr. INSLEE. Thank you. I want to thank the families.

My mom had kidney failure. I am particularly sensitive to the grief this is causing your families and all the families in the dialysis community. Your efforts here really will, I hope, pay off in getting the government to act.

Listening to the testimony, I reflect, though, can you imagine what we would do if al Qaeda had put some foreign substance in heparin? Can you imagine what the threat level would go to? Can you imagine how the FDA would respond then? Can you imagine how we would quit being somnolent and actually do something to protect us from this nefarious stuff going on in China?

We would really act then; and I would just hope that we start to react with some degree of responsibility.

I want to ask Mr. Nelson: have you reviewed Dr. Woodcock's testimony?

Mr. NELSON. I did, sir.

Mr. INSLEE. And did you find anything surprising in there?

Mr. NELSON. Well, the most surprising part to me dealt with—and I say, literally, "surprised." I was not aware from listening to the press conferences and from the interviews that only Changzhou SPL was subject to an import alert.

Mr. INSLEE. Why is that surprising?

Mr. NELSON. Because we thought—one would have thought that all heparin intermediates and products containing heparin from China would have been subject to an import alert, would have been detained without physical examination, which is what an import alert is.

Mr. INSLEE. And as I understand it, there's been at least 12 separate companies that have identified as having a contaminant that went to at least 11 different countries; is that right?

Mr. NELSON. That's the FDA numbers.

Mr. INSLEE. And there's only one manufacturer that's been subjected to that import alert; is that correct?

Mr. NELSON. That's correct.

Mr. INSLEE. And why is that important? Why is that deficient? Maybe it's obvious, but I'll ask you.

Mr. NELSON. Well, it is because those products are detained automatically by Customs.

What FDA—I'm sorry—what Dr. Woodcock's testimony goes on to say is that there are U.S. importers, drug manufacturers, that use these intermediates—five of them, I understand—who have agreed to perform these tests that Dr. Burgess is talking about, these tests that identify the contaminant; and their supplies are going through without being stopped at all.

And for those other importers that have not agreed to do the test, the FDA has alerted its field offices to detain the imports as they come in to identify, detain them, and require that they be tested, but not put them into an import alert status.

So whether those imports are actually detected is much more subject to human error than if they were subject to an import alert.

Mr. INSLEE. Well, why would you possibly not—if you know there are 12 companies that have been involved in this, I can't see any justification for only putting one on an import alert. I mean, is there any rationale for that?

Mr. NELSON. Not that I know of.

Mr. INSLEE. And as far as the ones that have agreed to be tested, is that a matter of public knowledge?

Mr. NELSON. No. FDA has not identified the firms, or their sources in China, the companies whose active ingredients—active pharmaceutical ingredients—for heparin are going to be permitted through without being stopped.

Mr. INSLEE. And have the importers, the American companies that are using this material, have they been told which ones are having the testing—the Chinese companies, which ones of the Chinese companies are having testing and which ones are not?

Mr. NELSON. I don't believe so. I mean, the American drug manufacturers that make the final product that have agreed to perform these tests know who their suppliers are. Customs probably has been told to allow the products through that are going from those specific Chinese firms to the American firms. But nobody's been alerted outside of the involved parties.

Mr. INSLEE. So I want to make sure that I do understand this.

There are 12 Chinese companies that our Federal agencies have identified had used a contaminant, this chondroitin sulfate material. It's gone to 11 companies, but only one is on an import alert; is that right?

Mr. NELSON. That's correct.

Mr. INSLEE. And only one of those has been publicly identified?

Mr. NELSON. That's correct.

Now, there are two other American manufacturers who have been identified as having received contaminated heparin. Those names are publicly known, although they have not—well, that's not true. At least one of them has not experienced any adverse events. The other, I noticed, is being sued, in press accounts today.

Mr. INSLEE. Now, would you agree with me, knowing what we know, that this really does present an extraordinary and unnecessary risk for the American people with this knowledge base to allow so many holes in our net?

Mr. NELSON. It doesn't make a lot of sense to me. Perhaps it's because I don't really understand how secure they think the net is. But from our investigations around food and drugs, it's very problematic.

Mr. INSLEE. Well, this committee in our half-dozen hearings believe the net, if not shredded, has serious holes, particularly in China.

And one of my concerns, too, if you look at the melamine incident, this incident, you know, it just seems like there might be a temporary interest in these subjects that gets dissipated as time goes on. And that's why I think having an import restriction that is clear and unambiguous and identified for these 12 ought to have been the appropriate response. And I think you agree with me—I think.

But do you have any comments on that?

Mr. NELSON. Yes, sir. FDA resource limitations really come into play here. I haven't asked them, but I would suspect they're not doing many inspections involving wheat gluten from China right now. I mean, that was last year's crisis and, quite frankly, they put a full court press on that.

They have put a full court press on this heparin.

But they don't have the ability to sustain those. They don't have enough people. They don't have enough laboratory resources. They don't have enough expertise to do anything but respond from crisis to crisis.

And they do a relatively good job of responding during a crisis, once it's identified.

Mr. INSLEE. The manufacturers of the raw heparin, the smaller that—we've been told some of them are just sort of what I would consider unregulated operations. Is there any inspection protocol in the Chinese system for all of the raw manufacturing facilities?

Mr. NELSON. There's no Chinese regulation of the heparin facilities, or there wasn't, none that I'm aware of now, all the way through to the API producer. I mean, they don't regulate the workshops, they don't regulate the consolidators, and they don't regulate firms like API, like Changzhou SPL, that make the final API.

They are outside the system for two reasons. Basically, they consider anything that's not a finished drug manufacturer to be a chemical plant not subject to their pharmaceutical regulations. And if they don't manufacture for the Chinese market, drugs for the Chinese market, they're not registered either.

So none of these firms were even registered with the Chinese Government when they began production in 2004 without any inspection from us.

Mr. INSLEE. Did the finished manufacturer use this test routinely to identify the sulfate, the chondroitin sulfate; did they use that test routinely, internally, do you know?

Mr. NELSON. I know that until this outbreak they didn't. I mean, now they—now they test it.

SPL Wisconsin, for example, doesn't have the capacity to; and that's pretty big—exclusive to their business. But they have the University of Wisconsin that does the testing for them.

I'm not qualified to talk about the kinds of tests. But they certainly were not contained in the USP monographs of required testing prior to the discovery of this contaminant.

Mr. INSLEE. Thank you.

Mr. STUPAK. I thank the gentleman.

Let me thank this panel and then thank you for coming and helping us here today. I know it's been very, very difficult, and we certainly do appreciate it. And on behalf of the full committee and this subcommittee, we appreciate your willingness and your courage for testifying today. Thank you, and we'll dismiss you. Thank you very much.

I now invite our second panel of witnesses to come forward.

On our second panel we have Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. Dr. Woodcock is accompanied by Ms. Deborah Autor, who is director of the Office of Compliance at the FDA's Center for Drug Evaluation and Research, and Ms. Regina Brown, who is a Consumer Safety Officer in the Division of Field Investigations at FDA, Office of Compliance within the Center for Drug Evaluation and Research.

It's the policy of this subcommittee to take all testimony under oath.

Please be advised that witnesses have the right, under the Rules of the House, to be advised by counsel during your testimony. Do any of you wish to be advised by counsel?

The indication is no.

Therefore, I ask you to rise, please raise your right hand and take the oath.

[Witnesses sworn.]

Let the record reflect the witnesses replied in the affirmative.

Each and every one of you are now under oath.

We will begin with an opening statement.

Dr. Woodcock, I understand you're going to give the opening statement.

Dr. WOODCOCK. Yes.

Mr. STUPAK. OK. We will hear a 5-minute statement. You may submit a longer statement for inclusion in our hearing record.

Dr. Woodcock?

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ROCKVILLE, MARYLAND; ACCOMPANIED BY DEBORAH M. AUTOR, DIRECTOR, OFFICE OF COMPLIANCE, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ROCKVILLE, MARYLAND; AND REGINA T. BROWN, CONSUMER SAFETY OFFICER, DIVISION OF FIELD INVESTIGATIONS, OFFICE OF REGIONAL OPERATIONS, OFFICE OF COMPLIANCE, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, NORTH BRUNSWICK, NEW JERSEY

Dr. WOODCOCK. Thank you, Mr. Chairman, members of the subcommittee. I'm Janet Woodcock, director of the Center for Drug Evaluation and Research at the FDA. I'm accompanied by Deborah Autor, who is director of CDER's Office of Compliance, and Regina Brown, who is an investigator and national expert in pharmaceuticals from FDA's Office of Regulatory Affairs.

Thank you for allowing me to discuss the important issue of the contamination of the U.S. heparin supply and its implications for our ability to maintain drug quality in the United States.

First, I would like to extend my deepest sympathies to the families of patients who were harmed by this contaminant. Patients who are dealing with life-threatening or chronic illness should be able to trust that life-saving medicines are of the highest quality. FDA needs the help of Congress to make sure that a tragedy like this does not happen again. Unless we act, another catastrophe will occur.

The U.S. drug supply has long been one of the world's safest. In fact, Americans may have forgotten that our drug supply was once dangerous and that great vigilance is required to maintain its current safety. In some parts of the world, consumers purchasing a medicine may have a 50 percent chance of getting a product that is not what's on the label.

The reliable quality of U.S. drugs is a result of a framework that was put in place over 60 years ago by Congress and implemented by the FDA to control and regulate the manufacture and movement of pharmaceuticals in the United States. However, since that time, there have been dramatic changes in the way drugs are produced and used.

First, many more Americans are taking many more medicines and relying on those medicines to maintain their health. The number of pharmaceutical products on the market has grown very rapidly; thus, the risk posed by quality problems and the complexity of regulating pharmaceutical quality have grown as well.

heparin is a good example of this. Heparin is not simply used by specific individuals to treat a specific condition. It's ubiquitous in health-care settings. Heparin is found in hospital wards, outpatient clinics, in emergency rooms, operating rooms, cath labs, dialysis centers, and even in home-health-care settings. Heparin is used in medical devices, and it's part of in vitro diagnostic agents. A problem with heparin thus has a potential to have widespread impact on our population.

Second, the sites of production of pharmaceuticals have changed. FDA has traditionally been configured to regulate a domestic industry using a field force that's located in district offices around the United States to perform inspections. Over the past 15 years, the majority of active pharmaceutical ingredient manufacture and actually increasing amounts of finished drug product manufacture has moved off our shores, been outsourced.

For example, generic drug applications processed in 2007 at the FDA referenced over 1,000 foreign sites; 450 of those were in India, 497 of those were in China for API manufacture of those generic drugs. And only 151 of them were in the United States. The rest were in other countries around the world. The FDA of the last century is not configured to regulate this century's globalized pharmaceutical industry.

Third, the complexity of modern manufacturing arrangements require more sophisticated oversight methods on the part of regulators. Currently, some generic drug applications submitted to FDA may reference up to 15 different facilities that contribute or could contribute ingredients to the finished product. As has been seen with heparin, intermediates and products can move through a complicated web of distribution and processing. Contaminated heparin from China actually ended up in a large number of different products around the world.

More sophisticated IT approaches are needed to monitor these supply chains. For example, as the GAO and this subcommittee has pointed out, we must have the ability to verify drug products that are being imported to make sure they should be allowed to enter the United States. In the past 5 years, the number of drug import lines, individual shipments, coming into the U.S. has grown from 140,000 to 312,000, approximately. Our current nonautomated approach to entry screening cannot continue. We need to be able to assure that both the product and the site of manufacture are acceptable before any drug gets into our country.

Finally, in the face of all this growth and change, FDA's relative inspectional resources have diminished. The number of foreign sites making drug products for import into the United States has more than doubled since 2001, but our inspectional coverage, which was already dangerously low and was discussed with this subcommittee in 2000, has declined by 35 percent in the same time period.

But this situation can be addressed. The remedy is simple. All parties throughout the chain, from production of API and other ingredients through brokers, distributors, importers, to finished product manufacturers, must be responsible for assuring the quality and integrity of the products they produce or handle, and FDA must have the tools to hold them accountable. These tools include resources, authorities, and scientific capacity to make sure this system is doing what needs to be done.

We must build a new system for pharmaceutical quality for the 21st century and prevent a tragedy like heparin from happening again. Thank you.

[The prepared statement of Dr. Woodcock follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

JANET WOODCOCK, M.D.
DIRECTOR
CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES

APRIL 29, 2008

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to discuss the important issues related to FDA's ongoing heparin investigation, in particular, and more broadly, the safety of drugs and pharmaceutical ingredients imported from countries outside the United States.

FDA's mission is to ensure that safe and effective new drugs, devices and biologics are made available to American consumers and that drugs, devices and biologics on the market remain safe and effective, regardless of where they are produced. I want to reiterate today what FDA Commissioner von Eschenbach has stated previously before this Subcommittee: we at FDA are fully committed to strengthening the drug safety system as fast as available science and resources will allow.

In my testimony today, I will first provide background about and the status of the Agency's ongoing heparin investigation. I will then briefly discuss the challenges presented by the globalization of drug development and manufacturing and the steps the Agency is taking to address these challenges.

ONGOING FDA HEPARIN INVESTIGATION

Brief Overview

Beginning in January 2008, Baxter Healthcare Corporation (Baxter) recalled various lots of heparin, a blood thinning drug, following a spike in reports of adverse events, including deaths, associated with the product. On April 21, 2008, after many weeks of intensive investigation and laboratory analysis, we were able to establish a link between a contaminant found in heparin, oversulfated chondroitin sulfate, and the serious adverse events seen in patients given heparin. We have been able to trace the contaminant to 12 different Chinese companies and it has been found in heparin batches shipped to 11 countries. We have made substantial progress in this case and FDA investigators and scientists are continuing to work independently and in collaboration with the Centers for Disease Control and Prevention, Baxter, and many other private and public entities in this ongoing investigation. FDA continues to monitor its post-marketing safety database for additional cases and has contacted regulators around the world to determine whether similar events have been seen in other countries with similar products.

Agency Process

Upon learning of the unusual spike in adverse events, FDA assembled an Agency-wide response team. Our goal has been to investigate and find the problem, to keep the public informed about the status of the safety of the heparin supply, to work with international partners in defining the scope and nature of the problem, and to make sure that an adequate supply of heparin is available to patients who need it.

This is a far-ranging investigation in the U.S. and abroad. FDA has inspected Baxter's domestic facilities, examined heparin product in the U.S., and sent a team of FDA experts to China to conduct a comprehensive inspection of Scientific Protein Labs (SPL) in Changzhou, China, the facility that makes the active pharmaceutical ingredient (API) for the heparin recalled by Baxter.

FDA Development of New Test Methods

One of our first steps in the investigation was to analyze the product for any abnormalities. FDA worked closely with the manufacturer and experts in academia and private laboratories to carry out a thorough chemical analysis of the suspect products. Conventional laboratory testing did not initially identify the contaminant. FDA experts then developed new test methods using state-of-the-art technologies such as nuclear magnetic resonance, capillary electrophoresis, enzymatic kinetics, and bioassays. As a result of a disciplined systematic examination, FDA scientists identified the previously unknown contaminant in the heparin. Specifically, some of the heparin product and heparin API manufactured by Baxter's supplier, SPL, was contaminated by oversulfated chondroitin sulfate, a heparin-like product derived from animal cartilage.

Chondroitin sulfate is sold as a dietary supplement. The contaminant is a derivative of that chemical compound and is not approved or sold for any medical purpose. The derivative compound reacts like heparin in many tests, which is why the traditional release tests did not detect it.

The Agency then publicized information on the two FDA-developed tests, and recommended use of the tests to manufacturers and suppliers for screening heparin API. FDA posted these FDA-recommended test methods on its website.

Linking the Contamination to the Adverse Events

After identifying the contaminant, FDA scientists then attempted to determine whether the contaminant in the product could be causing the adverse events. On April 21, 2008, FDA announced a link, based on animal testing and analysis, between the adverse events and the contaminant found in the drug. On April 23, 2008, FDA shared this scientific information in two journal articles published on-line in the New England Journal of Medicine and Nature Biotechnology, *http://content.nejm.org/cgi/content/full/NEJMoa0803200* and *http://www.nature.com/nbt/extra/nbt1407.pdf.*

Import Alert/Import Bulletin

The Agency's first priority in the heparin situation is detecting any contaminated products and preventing such products from reaching U.S. consumers or to remove them from the U.S. market. On January 25, 2008, Baxter announced the voluntary recall of nine lots of heparin sodium injection 1000 units/mL 10mL and 30mL multi-dose vials. The company began recalling the lots on January 17, 2008, as a precautionary measure due to an increase in the number of reports of adverse patient reactions that may be associated with the product. On February 11, 2008, FDA issued a public health advisory to inform the public about reports of serious adverse events in patients who received bolus injections of heparin sodium for injection primarily from multiple-dose vials manufactured by Baxter, and to recommend measures that may help to minimize these risks if this product must be used due to medical necessity, *http://www.fda.gov/cder/drug/advisory/heparin.htm.* On February 28, 2008, Baxter announced that the company was proceeding with the voluntary recall of all remaining lots and doses of its heparin sodium injection multi-dose, single-dose vials and HEP-LOCK heparin flush products. On February 28, 2008, FDA issued a public health update regarding the extension of the heparin recall, *http://www.fda.gov/cder/drug/infopage/heparin/public_health_update.htm.*

On March 10, 2008, FDA announced that all heparin coming into the U.S. from Changzhou, SPL in China was subject to an Import Alert (Import Alert 66-40). This means that, as with other products subject to this Import Alert, FDA can detain Changzhou SPL's heparin API and refuse its admission into the U.S. until it is demonstrated to FDA that appropriate corrections have been made. On March 14, 2008, FDA issued an assignment to its field staff requiring examination and sampling of all heparin sodium API coming into the U.S., except sodium heparin API being shipped to firms where FDA knows the recommended tests will be conducted. This sampling assignment means that all heparin sodium API shipments are being sampled and tested before being used or sold in the U.S. All other heparin products are also subject to sampling and testing at FDA's discretion. Testing imported heparin products will help ensure patients and healthcare professionals that heparin is safe for its indicated uses.

Early Communication

FDA has communicated throughout this investigation with the press, Congress, healthcare professionals, and the public to keep these groups apprized of important findings and developments as we move forward in our investigation. Transcripts and recordings of media calls are posted on FDA's website to provide broad access to information about developments. These communications are consistent with our Early Communication commitment to provide the public with information on developing and ongoing public health issues at the Agency. In addition, FDA created a page on the FDA website that contains the latest up-to-date information on heparin. We are continually posting information on this site located at: *www.fda.gov/cder/drug/infopage/heparin/default.htm.*

International Collaboration

Our investigation confirmed that the contamination is not limited to Baxter's heparin. Contamination of the heparin supply is a worldwide problem. At this point, because of FDA's sharing of its test methods, contamination has been detected in heparin in at least 11 different countries involving many different suppliers. FDA's working hypothesis is that this was intentional contamination, but this is not yet proven.

While the contaminant was first identified in the U.S., the recall of this product is international in scope. FDA has notified key regulatory international partners, and we are working closely with our Chinese and European counterparts in the investigation. The recently signed Memorandum of Agreement (MOA) (described later in this testimony) facilitated FDA investigators going to China to perform an investigation. In addition, five individuals from the Chinese State Food and Drug Administration (SFDA) were present during the February 20, 2008, inspection of the Changzhou, SPL facility.

On April 17 and 18, 2008, FDA convened a meeting with international counterparts that have been working on the heparin issue to discuss laboratory analysis/data interpretation and good manufacturing practice (GMP) inspections. The meeting focused on: (a) the challenges of analytical approaches we are presently using and the challenges of interpreting the results; (b) leveraging and integrating the information we are amassing and resources we are spending on our respective GMP inspections/investigations related to this matter; (c) initiating discussions on developing appropriate international compendia standards for heparin that will help mitigate the chances of such contamination in the future; and (d) considering how we can work together to identify products that may be contaminated in the future and how we can prevent and rapidly detect such contaminations. Representatives from the regulatory authorities of Australia, Canada, China, Denmark, European Union, France, Germany, Italy, Japan, Singapore, and Switzerland attended, as well as representatives of the U.S. Pharmacopoeia, European Pharmacopoeia, and the Massachusetts Institute of Technology. FDA will continue its leadership on this issue through ongoing discussions with colleagues from around the world.

Medical Devices

In an effort to remain vigilant in their efforts to assure that the safety and effectiveness of heparin-containing devices and *in vitro* diagnostic devices are not compromised, FDA's Center for Devices and Radiological Health (CDRH) has been proactive and collaborative by forming an intercenter task force who have been in daily and weekly contact with CDER's heparin task force. The objective is to maintain consistency of Agency actions and communications with device industry, professional and public stakeholders.

Using a multipronged approach to identify suppliers and distributors for devices identified as either coated with heparin or which use heparin as part of the device or *in vitro* diagnostic device, CDRH's task force searched and analyzed the medical device adverse event database to determine the scope and extent of any reported events similar to those events reported for bulk heparin. CDRH has contacted manufacturers of medical devices that contain heparin or use heparin during the manufacturing process to alert them to the potential for their devices to be affected by contaminated heparin. To maintain continued vigilance, CDRH is also notifying manufacturers of these types of devices about recommended testing procedures and follow up actions to assure continued device safety and adequate adverse event reporting.

Assuring Availability of Heparin for Patients

During this recall, FDA has been able to assure healthcare professionals and patients that there are no shortages of this critical drug. Another U.S.-based heparin API manufacturer, APP Pharmaceuticals, was able to supply the vast majority of the U.S. market, and continues to do so.

Could FDA Have Prevented the Situation?

The circumstances surrounding the recent recall of heparin raised questions about FDA's ability to fully assure the safety of pharmaceuticals and pharmaceutical ingredients produced outside the U.S. However, previous testing methods were not adequate to detect the potential contaminant. In investigating the most recent heparin situation, FDA learned in January 2008 that Baxter received FDA approval to use the API manufacturer, Changzhou SPL in Changzhou, China, although FDA did not conduct a pre-approval inspection of the plant. The plant subsequently shipped product to Baxter. As FDA has acknowledged, FDA's failure to inspect the plant was the result of human error. FDA staff entering data into a database confused the name of the Changzhou plant with another plant that had been previously inspected.

There is no justification for the theory that contamination of heparin would have been prevented if the inspection of Changzhou SPL had occurred in 2004. Intentional contamination is difficult to detect during an inspection and, in any case, the contamination appears to have begun long after the inspection would have been completed. Moreover, heparin contamination is not limited to product from Changzhou SPL, so timely inspection of that one firm would probably not have prevented the problem.

Process Improvements

We believe that process improvements that are already underway will prevent future data entry errors like this. These improvements include additional training for those who do the data entry on which inspection assignments hinge, hiring new staff dedicated to this data entry, and putting procedures in place that will provide FDA with the necessary data from drug manufacturers in a user-friendly way.

Unfortunately, there are sometimes factors beyond our control that affect the integrity of a product, such as when someone intentionally contaminates a product. We hope that systems in place would discourage or detect such manipulation but it would be disingenuous for FDA to suggest that it would be feasible for the Agency to inspect every single production facility and every single product, and that such inspection would discover every single problem. The imperfection of any system is a primary driver for FDA's life-cycle approach to product regulation. We must be able to identify a problem, aggressively and decisively investigate its root cause, and intervene to minimize the damage and to prevent future similar events.

Our goal is, of course, to minimize the risks associated with the use of drug products to the greatest possible extent. FDA recognizes that drug safety relies on a foundation of drug quality. Improperly manufactured drugs and drugs that are contaminated or illegally marketed can cause significant harm to patients. For this reason, FDA devotes considerable effort to reviewing and monitoring drug manufacturing activities. We know how important it is for FDA to determine that facilities named in drug applications will meet FDA standards for marketed drug safety, effectiveness, and quality, no matter where they are located.

GLOBALIZATION OF DRUG DEVELOPMENT AND MANUFACTURING

FDA increasingly faces challenges due to globalization of drug development and manufacturing. Not long ago, most drugs were developed, studied, and manufactured in the U.S. Today we routinely review and monitor drugs – both innovator and generic – that are studied or manufactured, at least in part, outside the U.S. The supply chain for finished drugs and active pharmaceutical ingredients now frequently links to manufacturing sites in China and India. With the globalization of the supply chain, FDA faces an ever-growing number of brokers, traders, distributors, repackagers, and other players involved in the import of pharmaceuticals. The changing world – including the fundamental challenges of many different languages and protocols – requires FDA to devise and evaluate more complex risk scenarios and apply more sophisticated technologies to screen and evaluate drugs entering the U.S. to ensure their quality.

Our generic drug program illustrates the dramatic changes during the last 10-15 years. Since 1992, we witnessed a 400 percent increase in the number of foreign establishments named in generic drug marketing applications. Today, in India alone, there are nearly 25 times as many drug establishments as there were eight years ago. Yet, FDA must be able to determine that facilities named in drug applications will meet FDA standards for marketed drug safety and effectiveness, no matter where they are located. FDA is taking many important steps to provide this assurance.

IT Enhancements

One of the keys to protecting the American drug supply is for FDA to have up-to-date, complete, interoperable data systems. The Commissioner has stated before this Subcommittee that upgrading FDA's Information Technology (IT) systems is one of his top priorities. Last year, FDA hired a new Chief Information Officer (CIO) with experience in developing and managing innovative and cost effective multi-organizational scientific and business programs, re-engineering governmental processes and managing the reduction of duplicative systems.

Efforts are underway to centralize all FDA's IT systems. This centralized approach provides the CIO the authority and oversight of available IT resources to meet the challenges of the FDA in the 21st century. Coupled with resource planning and development activities, FDA's Office of Information Management has undertaken detailed succession planning to ensure that the IT organization that FDA is building for the 21st century remains reliable in support of FDA's mission and sufficiently flexible to accommodate the science and technology advances of the future.

Logistically, foreign firms are more difficult to track and more challenging to inspect than domestic firms because we cannot always easily gain access to the firms. In addition, the data we have regarding foreign firms is not always easy to confirm or check for accuracy. Foreign firms must register with FDA before shipping to the U.S. Because for most firms there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S., or discontinue shipping without any notice to FDA. The practice of registering without producing or shipping can create uncertainty at any given moment about the precise number of FDA registered firms from which to target inspections, often requiring secondary data-source checking.

FDA monitors the importation of drug products and the manufacturer of those products through its Operational and Administrative System for Import Support (OASIS) system.

However, our systems do not yet have the capability to automatically verify the accuracy of all of the information submitted.

The formation of FDA's Bioinformatics Board (BiB) in 2006 provided an important means of ensuring that business needs and public safety endeavors are equally met by Agency IT services. Members of my office are actively involved in the work of BiB and the Business Review Boards created under it. BiB oversees the quality and performance of information systems, including business decisions on prioritization, planning, and execution of Agency cross-cutting business automation projects, positioning the Agency to meet external demands while, at the same time, satisfying the needs of FDA programs.

INTERNATIONAL EFFORTS

International Agreements

Good public health protection demands much more than a solid inspection program to manage imports. Faced with an unprecedented increase in products from abroad, FDA has relied on augmenting our foreign inspection program and entry admissibility reviews with the pursuit of two significant international strategies for helping to assure the quality of these products: harmonization of standards through multilateral fora, and two-party (bilateral) agreements with other countries.

In general, FDA and other countries enter into harmonization initiatives to assure product quality while at the same time conserving human and financial resources and improving the efficiency of their operations. When nations can agree on scientific standards for establishing the safety, effectiveness, and manufacturing quality of pharmaceutical products, everyone wins. Sometimes, harmonization efforts among many nations do not address specific national needs. In such situations, FDA and its international counterparts find it mutually beneficial to enter into one-on-one agreements that allow them to share information and work closely together to solve specific problems.

On December 11, 2007, Secretary Leavitt announced the signing of a MOA between the United States and China, to improve the safety of drugs and medical devices. Some of the critical aspects of the agreement include: (1) all Chinese producers of items covered under the agreement for export to the U.S. must register with Chinese authorities; (2) the Chinese will adopt quality-assurance electronic tracking methods for certain products; (3) information sharing by providing timely notification to U.S. regulators regarding certain inspectional failures at drug manufacturing facilities and shipments of products that may be dangerous. In addition, the Chinese will facilitate and expedite inspections by FDA investigators of Chinese drug plants. The MOA covering drugs was instrumental in expediting FDA's entry into China to investigate the problems with heparin.

FDA has a variety of cooperative relationships with foreign regulators that support our efforts to manage the challenges presented by global production of drugs and biologics. A list of FDA's commitments appears on FDA's Office of International Programs, International Arrangements, *http://www.fda.gov/oia/agree.htm*.

Establishing an FDA Presence Abroad

On March 14, 2008, FDA announced that it had received approval from the U.S. State Department to establish eight full-time FDA positions in China, pending authorization of the Chinese government. FDA regards this as an important step forward in our plans to hire and place FDA staff in China over the next 18 months. In addition, FDA will be hiring a total of five local Chinese nationals. These staff members will enhance FDA's capacity to inspect Agency-regulated industry in China as well as improve our understanding and oversight. This initiative facilitates the building of stronger cooperative relationships with FDA counterpart agencies around the world and enhanced technical cooperation with foreign regulators. The overseas presence in China will also allow greater access for inspections and greater interactions with manufacturers to help assure that products that are shipped to the U.S. meet U.S. standards for safety and manufacturing quality.

Building FDA's capacity outside of the U.S. is the primary driver of FDA's "Beyond Our Borders" initiative which was described more fully in the Commissioner's testimony to this Subcommittee on April 22, 2008.

Educational Workshops

FDA also works around the world to help regulators and manufacturers understand modern drug standards. For example, my office conducted a series of educational workshops in China in December 2005 and April 2006 on current GMP (cGMP), in collaboration with the International Society for Pharmaceutical Engineering and Peking University. The workshops educated participants on current methods for compliance with cGMP to ensure effective cGMP programs and to further the common goals of FDA and providers of quality pharmaceutical products. The workshops were open to any professionals involved in the manufacture, control, and regulation of pharmaceutical products, including process/production engineers, manufacturing personnel, quality assurance/quality control and regulatory affairs professionals, consultants, regulatory investigators and cGMP compliance officials. Just last month, I taught workshops on cGMP and on prevention of contamination and counterfeiting to members of China's SFDA.

CONCLUSION

Ensuring the safety and efficacy of the drug products used by American consumers continues to be a top priority for FDA. Despite the challenges that face us, the American drug supply continues to be among the safest in the world. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.

Mr. STUPAK. Ms. Autor, do you want an opening statement?

Ms. AUTOR. No, sir.

Mr. STUPAK. Ms. Brown, an opening statement?

Ms. BROWN. No.

Mr. STUPAK. All right. Then we'll begin questions.

Dr. Woodcock, how long have you been—you were acting director and then director of CDER, so how long a time is that? You were acting director for a period; now you've recently been promoted as director of CDER.

Dr. WOODCOCK. Being under oath, I am very bad with dates, so I will give you an approximate time. In the fall in October, I believe, I was acting director of CDER, and recently I was made permanent center director.

Mr. STUPAK. Most of your time at the FDA has been in CDER, right, the Center for Drug Evaluation and Research?

Dr. WOODCOCK. Correct.

Mr. STUPAK. So how long have you been at CDER?

Dr. WOODCOCK. I was head of the Center for Drugs from 1994 to—I went on detail out of the Center for Drugs in 2004. Although I was still in the position, I wasn't acting in the position.

Mr. STUPAK. All right. Let me ask you this. You said you need help from Congress, Congress is trying to give you help. Have you made any opinion on the Dingell legislation which is pending? Have you rendered an opinion, is that a good piece of legislation as something we should pass to help out FDA?

Dr. WOODCOCK. We are evaluating the——

Mr. STUPAK. No, I'm asking you, have you made an opinion?

Dr. WOODCOCK. I haven't completed my opinion. I think it makes a good start.

Mr. STUPAK. OK. How about the Internet pharmaceutical legislation we've had for the last 10 years? Have you made any decisions on any of that legislation over 10 years, whether it's good or bad that Congress would help you out if we passed that legislation?

Dr. WOODCOCK. I don't have an opinion on that. That's more of a legal issue, I believe.

Mr. STUPAK. OK. Well, you're the director, and you know you said you need help from Congress. You're here under oath. So we're trying to ask you, what is the help you need?

How much money did you request for inspections this year, for foreign inspections of plants?

Dr. WOODCOCK. In 2009?

Mr. STUPAK. Sure, for 2009, in your role.

Dr. WOODCOCK. I believe there was a $5 million increase.

Mr. STUPAK. A $5 million increase, at $45,000 per inspection overseas, is not very many inspections.

Dr. WOODCOCK. That was for the criminal investigators.

Mr. STUPAK. Just the criminal investigators. How about for inspections of drug plants overseas?

Dr. WOODCOCK. I don't believe there is a provision for any increase.

Mr. STUPAK. Kyle, put up this map, would you?

So there's no increase in inspections, but yet inspections seem to be the key here, is it not?

Dr. WOODCOCK. Inspections are one essential piece. We need to——

Mr. STUPAK. OK. Now, the FDA inspects in the United States every 2.7 years. With China, it's 30-plus years, correct? Correct?

Dr. WOODCOCK. Well, 30-plus—I think 2.7 you would say correct. 30-plus is an extrapolation. As a scientist, I have to tell you we don't get there often enough.

Mr. STUPAK. Well, let me tell you, there's 714 plants that we know in China right now. You inspected, at most, 20 last year. You do the math: 20 of the 714, how many years will it take you to inspect one of these plants? My math, it's about 40 to 50 years. I'm being kind at 30 years, am I not?

But yet you, as director of CDER, who is responsible for this, you just testified you have not asked for extra money for inspections. So is this acceptable, every 30 years?

Dr. WOODCOCK. I believe that FDA needs more inspectional resources. That is what I just said in my opening statement.

Mr. STUPAK. Sure. We're trying to help you, but you won't tell us what you need. So how can Congress help you if you won't tell us what you need?

Kyle, would you put up the first map, please, that we had today?

Let me ask you this, Doctor. There's no doubt that these plants should have been inspected in China, right, Changzhou SPL?

Dr. WOODCOCK. That was an error on our part.

Mr. STUPAK. Right. I realize that. How about the consolidators, should they be inspected by the FDA?

Dr. WOODCOCK. I will defer that to Deb Autor.

Mr. STUPAK. Ms. Autor, should consolidators be inspected?

Ms. AUTOR. In the normal course, consolidators would not be our first priority for inspection, but, ideally, yes, we would look at them as well.

Mr. STUPAK. OK. How about brokers, should they be inspected, Ms. Autor?

Ms. AUTOR. I think that the best way to ensure the integrity of the products coming through from the workshops to the brokers to consolidators and, ultimately, the API manufacturer and finished dosage manufacturers, have everybody in that supply chain responsible for the quality and integrity of the products.

Mr. STUPAK. The workshops should also be inspected, right?

Ms. AUTOR. If we have the resources, I think that we would be happy to go to the workshops.

Mr. STUPAK. What is the amount of resources you need to do that?

Ms. AUTOR. Excuse me?

Mr. STUPAK. What is the amount of resources you need to do that? The Commissioner didn't know last week. The head of CDER doesn't know. Maybe, Ms. Autor, you would know.

Does anyone know what the resources the FDA needs to do their job?

Dr. WOODCOCK. If you're asking a very specific question about what do the resources need to, what, inspect every plant in China or every foreign facility every other year?

Mr. STUPAK. You're the expert. I'm asking you. What do we need?

Dr. WOODCOCK. To answer your factual question, I believe that to do a—there have been multiple estimates. Jane Haney gave you an estimate in writing in 2000 that said it would be $23 million. I think that was a very low estimate that isn't correct. And, of course, the number of facilities have at least doubled.

Mr. STUPAK. Do you have a number or not?

Dr. WOODCOCK. Yes.

Mr. STUPAK. Please give it to me.

Dr. WOODCOCK. I believe the number to inspect every facility around the world outside the U.S. every other year would take about $225 million.

Mr. STUPAK. And do you realize the Dingell legislation, if passed today, would bring in about $300 million a year for drug inspections? Are you aware of that?

Dr. WOODCOCK. I didn't do the math.

Mr. STUPAK. Are you aware it would also bring in $600 million a year for food safety?

We've had seven hearings on that this year. So why aren't you endorsing the Dingell legislation?

Dr. WOODCOCK. I am giving you my technical——

Mr. STUPAK. Sure. Let me ask you this question. I know you can't give an opinion on Dingell legislation. We've been waiting for it many years.

Dr. WOODCOCK. May I tell you one more thing about this?

Mr. STUPAK. Sure.

Dr. WOODCOCK. All right. It would be important, I think, to have the same level of coverage of a domestic inspection as foreign.

Mr. STUPAK. Absolutely. We've been saying that for years.

Dr. WOODCOCK. It would also require an increase of about $100 million over and above the figure I just gave you. Now, I believe that——

Mr. STUPAK. Very good. And the FDA asked where this 2009—your total budget for inspections is $9 million, and next year you go to a whopping $11 million. Not enough to make a drop in the bucket.

How many firms ship active pharmaceutical ingredients, APIs, from overseas to the United States? How many firms are there?

Dr. WOODCOCK. As you know, that's another thing that we need improvement on.

Mr. STUPAK. Right. You really don't know, do you? It's somewhere between 3,000 and 7,000. Isn't that correct?

Dr. WOODCOCK. It is most likely between 3,000 and 7,000, most likely on the lower end.

Mr. STUPAK. That's really close. Let me ask you this. What's the number of heparin producers in the world? Do you know that? Can you narrow that one down for us?

Dr. WOODCOCK. The number of heparin producers?

Mr. STUPAK. Of the active pharmaceutical ingredients that ship it to the United States. How many plants worldwide are making heparin API for shipment to the United States?

Dr. WOODCOCK. Do you know the answer to that?

Ms. AUTOR. I don't know.

I do believe that our total foreign inventory is about 3,300. That's the best number for foreign manufacturing. About 80 percent of them are——

Mr. STUPAK. How about on heparin here? How many do you have on heparin?

Ms. AUTOR. We wouldn't have any reason to count worldwide heparin suppliers. We would only be focused on what we're shipping to the United States.

Mr. STUPAK. After the heparin outbreak, you wouldn't go back and check to see how many plants are producing heparin for the United States?

Ms. AUTOR. For the United States, yes.

Mr. STUPAK. Yes, active pharmaceutical ingredients for the United States. How many are there?

Ms. AUTOR. I would have to check the exact number.

But with heparin, what we have done is put in place a sampling assignment so that we are confident of the quality of all the heparin brought into the United States.

Mr. STUPAK. Sure. But how many heparin manufacturers are there in China? Can you answer that one?

Ms. AUTOR. I don't have that number.

But, again, the point is that we have checked on the quality of the heparin coming into the United States.

Mr. STUPAK. But how do you know that if you don't know where it's coming from? How can you inspect a substance if you don't know where it's coming from?

You have 300-and-some ports that allow product in this country. You have 94 inspectors, at most, in the FDA. Your chances of getting caught are one in three. And you don't even know where it's coming from.

Ms. AUTOR. What we have in place is a sampling assignment at the border, which stops all heparin coming into the country and holds it until we're satisfied.

Mr. STUPAK. And who makes that decision at the border?

Ms. AUTOR. That's made by the import inspector. But, again, we have——

Mr. STUPAK. And who is the import inspector? Do they work for the FDA or the Customs-Border Patrol?

Ms. AUTOR. That decision would be made by the FDA.

Mr. STUPAK. And earlier testimony showed they have 30 seconds to make that decision, right? But we don't even recognize the name of the company that's sending it from China, because we don't know who it is. Because you don't know how many plants manufacture heparin active pharmaceutical ingredients in China for shipment to the United States, do you?

Ms. AUTOR. I'm confident, sir, that all the heparin coming into the border is being stopped and checked to see whether it's being tested for the overly sulfated chondroitin sulfate.

Mr. STUPAK. And are you just as confident you know of every heparin producer in the world that's shipped products to the United States?

Ms. AUTOR. I don't have that information at my fingertips, but, again——

Mr. STUPAK. So how can you be confident? If you don't know who is shipping it out, can you be confident you're catching it at the border?

Let me ask you this. Can you tell us what five companies have agreed to test its products, its heparin products? What are the five companies?

Ms. AUTOR. There are actually six, but I don't have——

Mr. STUPAK. OK. What are the six?

Ms. AUTOR. I don't have their names at my fingertips now, sir.

Mr. STUPAK. Dr. Woodcock, do you know the six of them that have agreed to test its products?

Dr. WOODCOCK. The heparin sodium for injection, the product that is used in dialysis——

Mr. STUPAK. OK. Right. Do you know the six companies?

Dr. WOODCOCK. We know who they are. I don't have their names in front of me.

Mr. STUPAK. All right. Now, look, you're the experts. You don't know, so how is the inspector at the border going to know? You're the experts. You've done an investigation. If you can't tell me the six companies, how is the port inspector at the border, who has 30 seconds to make up their mind, going to know the names of them?

Ms. AUTOR. Because they do know. They are told to consult with our center import people who are responsible for those——

Mr. STUPAK. Well, let me ask you this. Can you tell us the top 12 Chinese companies that have produced contaminated API, heparin API? Can you tell us those companies?

Ms. AUTOR. I do know those 12 companies. However, I do not know whether that is public information. I would be happy to provide that to the committee if the committee makes a request for that.

Mr. STUPAK. Do you think the American people don't have a right to know which people produced contaminated heparin for shipment to the United States?

Ms. AUTOR. I do not know whether I have the authority to release that information. But, again, I would be happy to release it if the committee requests it.

Mr. STUPAK. I just requested it. So would you get it to us, so we can put it out publicly, so at least the American people know?

All right. Let me ask you this.

My time is just about up.

Ms. Autor, at last week's hearing on the FDA foreign inspection program, the Commissioner suggested that the FDA's inspection would not have detected the tainted heparin. Of course, we don't know that, because we never inspected it. Nevertheless, FDA's team found that the way this plant was operating essentially made the products unsafe for U.S. market.

Doesn't this suggest that, had the inspection been scheduled at the facility as part of its normal pre-approval process, the FDA may have found that this plant was unable to operate safely; thus, it would have required adjustments to the facility's operations, which may have impacted the outcome of today's hearing?

Ms. AUTOR. I do not believe we have any reason to think that. As you know, Mr. Chairman, the inspection that was not done was in 2004. The contamination that we have seen with heparin did not occur until at least 2006, 2007.

I think, in all likelihood, what would have happened is we would have inspected, we would have found GMP problems, they would have corrected them, and Changzhou SPL would have gone on to become the heparin supplier for Baxter, as they did.

We do know that we have companies that we did inspect that were heparin suppliers to China that were in compliance but, nonetheless, became purveyors of contaminated heparin. So complying with GMP——

Mr. STUPAK. But if you would've had your 2.7-year inspection like you do in this country, you probably would have caught it then, right?

Ms. AUTOR. I don't have any reason to think that. Again, we did inspect firms——

Mr. STUPAK. How about do you have an opinion on this one? If you don't inspect a plant until every 30 years or 40 years, what's the deterrent effect, then, of inspecting plants?

Ms. AUTOR. Sir, I would be happy to go and inspect a lot more of these firms a lot more often if I had the resources.

Mr. STUPAK. Right, but you guys can't tell me the resources you need either.

So let me go back to ask that question. If you don't inspect the plant 30 to 40 years, it encourages, as opposed to discourage, adulteration of drugs as we have here in heparin, right?

Ms. AUTOR. We absolutely need in place a better system for inspections, as well as a better system of corporate responsibility throughout the supply chain. There's no question about that.

Mr. STUPAK. All right.

Just one more. I'm very disappointed, Dr. Woodcock and others, that this is the second heparin hearing this week. I would think that, by now, you would anticipate our questions and have some answers for us, like inspections, number of plants that produce it, number of heparins coming into the United States from different plants from overseas. I hope we can do a better job at being prepared.

With that, I'll turn to Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman.

As you all know, and I think it may be important to take this back to the Administrator, that there's going to be a bill that's going to be presented that's going to move. You've identified, even in your opening statement, that there are IT issues, product and site manufacturing and testing problems. You've identified resource constraints.

I think my colleagues on the other side are trying to handle these in a manner that we ought to take seriously. And the Agency ought to be prepared to engage with the Committee so that we get to a point where—and so, I'd just ask—these committees are interested. This is the Oversight and Investigations. We're not the authorization committee of substance. However, the folks and the investigators on both sides are pretty well deep into the weeds of this. And I would hope that the committees would turn to their expertise on the analysis on both sides as to how we can start addressing this.

So I want to encourage you, which I will do to the administration, to start engaging to help us figure out how best to answer these questions. Because we can do so in a bipartisan manner. If you don't come to the table, then you may not have a chance to really impact it in a direction that you think is going to be helpful. So I'd just throw that out.

I do want to follow the Chairman's line of comments, just on the porcine components that are used in so-called low-molecular-weight heparin and pancreatic supplement, certain insulins, poractant-alpha, for treatment of respiratory diseases, syndromes and other neonates and stuff that I don't even have any idea what I'm talking about, but they sound very important and probably as important as the heparin use.

Because of this specific experience—and we're talking about all these drugs that are coming out of pigs and all these ingredients that help us do all these great advances—what has the FDA done to check that these and other porcine-sourced API products regulated by you all are not subject to adulteration?

Dr. WOODCOCK. That's a good question. For low-molecular-weight heparin, it is sourced from heparin, regular heparin, much of which is sourced from China, the API. The low-molecular-weight heparin supplies in the United States have been tested and are not contaminated. They've been tested using the FDA test. Around the world, there is significant contamination of the low-molecular-weight heparin supply, and we are in contact with regulatory authorities around the world to deal with this situation.

For pancreatic enzymes, we are actively looking at that. We have been looking at that for some time. For the surfactant product, I think the newer drugs have much more sophisticated control tests and identity tests on them, and so they are subject to a lot more testing before they're released than an older drug like heparin. And so I think we can be confident that that product is tested adequately.

Mr. SHIMKUS. And when you use the terminology "looking at," what do you mean? I mean, do you mean testing? Do you mean looking at early in the process, through the process, a final lab test? What do you mean by "looking at"?

Dr. WOODCOCK. We are looking at the capacity—we have been doing this, actually, for a while for the pancreatic enzymes, and we are looking at the capacity to process, to screen out contaminants. Those processes and those products have tests of potency that are somewhat more specific than the heparin test was.

So we are scientifically evaluating it for its robustness and its vulnerability to something like this.

Mr. SHIMKUS. I hate to ask this question, but in "looking at," did you increase your inspections of plants overseas? Is that part of the "looking at"?

Dr. WOODCOCK. We have been focusing our inspectional resources right now on the heparin issue. We certainly have been putting this into our algorithm of something we will need to get to.

Mr. SHIMKUS. Have we increased the inspection of overseas facilities that produce heparin? Is that part of the "looking at"?

Dr. WOODCOCK. Oh, yes, of heparin, yes.

Mr. SHIMKUS. What about other porcine—what's the terminology, porcine supplements?

Dr. WOODCOCK. Source product.

Mr. SHIMKUS. Source product.

Dr. WOODCOCK. Certainly, we will do that.

Mr. SHIMKUS. We will, but we have not?

Dr. WOODCOCK. We are focusing on heparin, but we have had the same thought that you have had.

Mr. SHIMKUS. This another issue that we are trying to get our hands around, as far as Dr. Burgess followed up on the questions, that this, somewhere along the chain, intentional dilution or hiding of, not a pure supplement or a pure additive or whatever the right, the chemical term is for this.

Part of the debate has been that the number of pigs available, I mean, or the lack thereof, caused the price to go up, and so someone may have used a dilution aspect to make sure that they could still meet or even sell what—and then, again, there's where the sinister aspect of this—in a way in which it hid from the test.

Again, going back to resources—and I think the point of many of us will be we want to—you almost have to, in these countries in which we're importing drugs from, we almost have more certainty along the whole chain of events.

Was there anything that raised a flag to the FDA about the supply of pigs, that that may trigger nefarious activities in the supply chain?

Dr. WOODCOCK. Deb, would you like to take that?

Ms. AUTOR. Sure.

There's certainly more that FDA could do here in terms of having tools and resources to address this: a dedicated foreign inspectorate, inspecting importers, administrative destruction authority. There's a lot of things we could do to be stronger here.

But, frankly, I do not believe that it would be reasonable to expect the agency to be monitoring the price of heparin and to see that red flag. That responsibility should fall on manufacturers. They have the best ability, the best information, the best incentives to ensure the integrity of the quality of their products, and they should be paying attention to that.

And when the price starts to go up, they should think either that something is wrong with the supply chain or that there is an opportunity for something nefarious to happen, given that price shift.

But again, it has to be the manufacturers. FDA will not be able to keep up with that for every product that's in the marketplace.

Mr. SHIMKUS. Let me just follow up with this question.

As we know, industry, they have an interest in making sure that they don't sell bad products, whether that's—and I think there are some folks that will say they're all going to go after the mighty buck and they are not going to care. And there's some of us that believe that, no, they do care, because their brand name is important, their product is important, the litigiousness of the society and the lawsuits, especially in this country, will make them pay dearly for failure.

What we're going to have to address—and this isn't a legislative hearing that's going to happen on the language of the bill. But what we're going to have to address is, how do we marry—there's going to be talk about certification of inspectors or whether they're FDA inspectors or do you all certify them, and then there's an inspection of the inspectors and all sorts of things.

But again, you're coming in saying that we need resources, we need IT, we need a better inspection regime. And I, again, want to throw that back to you all to—and I see the Chairman of the full committee is here. And, you know, I can guarantee you that you would rather be in the room helping than on the receiving end. And that's what I'm going to still encourage you to do.

Let me finish by—the Chinese have said that contaminated heparin from China did not cause the adverse reactions in the United States. You have said that the oversulfated chondroitin sulfate found in the contaminated heparin could have been the cause. What should we make of this disagreement, and who is right?

Dr. WOODCOCK. The Chinese authorities had tested one lot of material that they found to be negative for the contaminant. And that lot was implicated in adverse events. We have tested that lot in three labs and have found a contaminant, and we also agree that the lot is implicated. But that was the basis of the Chinese scientists' reasoning that the contaminant could not have been associated with the adverse reactions.

Mr. SHIMKUS. My last question—and I appreciate the extension of the time—is, what does this attitude suggest about China's appreciation of the seriousness of the adulteration in the first place?

Dr. WOODCOCK. Well, I think this was a disagreement over analytical results. But we do stress, we agree, that products should not have been contaminated under any circumstances, regardless of whether there were any adverse events associated with it or not.

Mr. SHIMKUS. And I think we can end it up by saying—we use it all over the place on the Hill—we need to trust but verify. And the question is, how much are we verifying? And that's part of the debate.

Mr. STUPAK. I thank the gentleman for his questions.

Mr. Dingell, any questions?

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy.

These questions for Ms. Autor and for Dr. Woodcock, they will require only a yes or a no. And we will begin in each instance with Ms. Autor.

Is it your view that FDA should inspect foreign drug facilities more frequently than it does now, yes or no?

Ms. AUTOR. Yes.

Mr. DINGELL. Dr. Woodcock?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Given that FDA only inspects foreign drug facilities on average once every 13 years, in your opinion, does FDA need a substantial increase in resources to inspect foreign drug manufacturers at a frequency similar to that which it investigates or reviews the behavior of domestic manufacturers?

Ms. Autor?

Ms. AUTOR. Yes, although the frequency should be risk-based.

Mr. DINGELL. Dr. Woodcock?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Is it your view that FDA should have the ability to deny entry to imports if the facilities in which they were produced refuse, delay, or impede an inspection?

Ms. AUTOR. Yes.

Dr. WOODCOCK. Definitely.

Mr. DINGELL. Is it your view that all drug facilities should be subject to an initial inspection before they can begin shipping products or ingredients?

Ms. AUTOR. Yes.

Mr. DINGELL. Yes or no?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Now, in your opinion, would requiring drug facilities to register and pay a fee on an annual basis to help clean up FDA's databases and to provide for a more accurate accounting of firms providing drugs to American manufacturers—Ms. Autor?

Ms. AUTOR. In my opinion, yes, that would be a good step.

Mr. DINGELL. Dr. Woodcock?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Is it your view that having a unique identifier attached to each drug facility and each importer would allow FDA to move more quickly to track down manufacturers in the event of a safety incident?

Ms. AUTOR. Absolutely.

Dr. WOODCOCK. Crucial.

Mr. DINGELL. In your opinion, would it be useful for FDA to be able to explicitly require manufacturers to know and to verify the safety of their supply chain; in other words, to verify that the ingredients that make up the drugs they sell to the American people have been manufactured, processed, shipped, and warehoused in such a way that the quality of the product has not been compromised?

Ms. AUTOR. Yes.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Now, Dr. Woodcock, there are some questions—oh, by the way, I wanted to say something to Ms. Brown.

Ms. Brown, your good work is known to the Committee, and I want to commend you for it. Thank you.

Ms. BROWN. Thank you.

Mr. DINGELL. We need folks like you in Government service. Thank you.

Ms. Woodcock, in your testimony you note that Changzhou SPL has been added to import alert 6640. This is a general import involving a number of foreign firms that FDA has found to be so out of compliance that their products cannot enter until FDA has reinspected and found them to be radically improved. Is that correct?

Dr. WOODCOCK. Me?

Mr. DINGELL. That's to Dr. Woodcock, please.

Dr. WOODCOCK. That's my understanding, yes.

Mr. DINGELL. But crude heparin, the heparin active pharmaceutical ingredient or finished heparin products are not under a general import alert like, say, the five species of fish from China that went on import alert last summer. Is that correct?

Dr. WOODCOCK. That's my understanding. My understanding is there's a different legal standard, as was alluded to earlier, for an import alert.

Mr. DINGELL. Now, in your testimony you state that FDA has identified a total of 12 Chinese sources of contaminated heparin going to 11 different countries. Is that correct?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Now, I'm going to try to understand this. Some of the importers you are allowing, then, in Food and Drug to bring products from Chinese sources are being permitted to do so because they voluntarily agreed to apply the tests that you at Food and Drug have developed for counterfeits. Is that correct?

Dr. WOODCOCK. That's correct.

Mr. DINGELL. But you have not identified publicly the importers or their Chinese suppliers. Is that correct?

Dr. WOODCOCK. That's correct. Some of that we received under confidentiality agreements with other countries.

Mr. DINGELL. All right. I'm going to ask that you submit those names to the Committee for the purposes of the record.

Dr. WOODCOCK. Certainly.

Mr. DINGELL. Now, can you tell me—you said that you've received these under confidentiality agreements? Is that the reason?

Dr. WOODCOCK. Yes.

Mr. DINGELL. What is the authority for you receiving that kind of information under confidentiality agreements? Why is it that you can't just receive the information? Why are you constrained in what you may do with it or the circumstances under which you can receive it?

Dr. WOODCOCK. My understanding is that we have signed these agreements with other countries in order that they would give us the information and that we would be able to give them the information that——

Mr. DINGELL. Have you no other way of getting this information?

Dr. WOODCOCK. That has been explored extensively because we really would like to have free interchange with international regulators. However, we are constrained by our own laws that restrict how much information we can release publicly. And for us to give——

Mr. DINGELL. Let me try to simplify this, because that clock is very cruel. Are you telling me you have no other way of compelling the production of this information?

Dr. WOODCOCK. Some of it involves foreign firms that have never shipped into the United States.

Mr. DINGELL. I know. Have you no other way of getting this information? I want you to have the information.

Dr. WOODCOCK. Thank you.

Mr. DINGELL. Don't you think you need the information?

Dr. WOODCOCK. It's what other countries give us voluntarily right now, because we have these agreements.

Mr. DINGELL. Dear friend, I'm trying to get some answers to these questions, and you must cooperate with me.

Are you barred—why are you not able to just say, "We want this information"?

Dr. WOODCOCK. Actually, my understanding is the concern is, if we release—we have lots of confidentiality laws in the United States that prevent us from releasing information we have publicly, right? And Congress passed those laws. If——

Mr. DINGELL. So you need then to have this law changed so that you can just go in and say, "We want the information." is that right?

Dr. WOODCOCK. If we could freely give information to other countries, they would be more willing to freely give it to us.

Mr. DINGELL. We're going to see that you get the information.

Now, is it correct that there are other importers that have not agreed to voluntarily test their Chinese imports of heparin? In other words, you've got some companies that have not agreed to voluntarily test the imports of Chinese heparin.

Ms. AUTOR. The major suppliers of heparin have all agreed to test that. Any other heparin coming to the border is stopped and tested by us.

Mr. DINGELL. So you have some that have not?

Dr. WOODCOCK. May I clarify that, please?

Mr. DINGELL. I'm sorry? Well, yes. Just answer the question, yes, please.

Dr. WOODCOCK. I do not want to make patients in the United States feel afraid, all right? The heparin for injection, as I was trying to say earlier, that is the kind of heparin used in dialysis labs and so forth, that heparin is all being tested, and we know who the manufacturers are, and we know who the suppliers are. There are many other types of sources, though, that go——

Mr. DINGELL. Right. Let's try and make this very simple. Yes or no, you have companies that have not agreed to voluntarily to test Chinese imports? Yes or no?

Ms. AUTOR. I don't know if they have refused or if we have not had that discussion. But, again, the contaminant is detectible, and all heparin coming in is being tested.

Mr. DINGELL. But they have not done so. Is that right?

Ms. AUTOR. I'm sorry?

Mr. DINGELL. But they have not done so. Is that right?

Ms. AUTOR. At this point, there are suppliers with whom we don't have that agreement. Compounding, for example.

Mr. DINGELL. All right. So you have some that have not. You don't know why?

Ms. AUTOR. I am not engaged in those details, sir, no.

Mr. DINGELL. All right. Will you procure the information and tell us why?

Ms. AUTOR. Certainly.

Mr. DINGELL. And I want you to submit to us the names of the companies of which you know that have not agreed to voluntarily test their Chinese imports. Please submit that for the record.

How many of them are there, please? Do you have any idea?

Ms. AUTOR. Again, I do not manage those details on a day-to-day basis, sir.

Mr. DINGELL. All right. So the situation, then, is that these importers are being permitted to continue importing even though they've not signed the agreements that the others have done to require voluntary testing. Is that right?

Ms. AUTOR. All of their heparin is being stopped and tested. And, again, the contaminated product has been recalled, and the firms that we know that have been affected, that have been associated with contaminated heparin in the U.S., have stopped shipping that contaminated heparin.

Mr. DINGELL. OK. So you have stopped them, and you are inspecting them. And if I understand it correctly, FDA entry reviewers now have an opportunity to investigate or review these substances as they come in for a total of 30 seconds. Is that right?

Ms. AUTOR. No, sir. I think that——

Mr. DINGELL. That's the average that they have.

Ms. AUTOR. That is correct. But, for this situation, I am certain that they are stopping it and fully considering it and consulting with others in FDA to make sure that there is not contaminated heparin entering the U.S.

Mr. DINGELL. Now, that's a wonderful statement, but how are you certain?

Ms. AUTOR. Because I believe we have a system in place that does that.

Mr. DINGELL. How can you assure me under oath that you are able to see to it that these are properly investigated? Now, you're under oath. How can you give me that assurance?

Ms. AUTOR. Yes, sir. We have a sampling assignment in place which gives direction to the people in the field that they are to stop the heparin and ensure that it is being tested before it enters commerce.

Mr. DINGELL. So you are telling me, then, that your instructions to the field are just as effective as an import alert?

Ms. AUTOR. They should be, yes, sir.

Mr. DINGELL. Can you make that statement again under oath?

Ms. AUTOR. Yes, sir.

Mr. DINGELL. Boy, oh boy, oh boy, you have great confidence in your oath.

Now, you have heard, then, of dangerous contaminated product that has come in from many sources in China. You have not gotten assurances from many of the importers that they will test the raw materials or the heparin that's coming in. And FDA has placed only one firm on import alert.

Please tell me how that is protecting the American public.

Ms. AUTOR. Again, sir, I believe that there is adequate protection with respect to heparin coming into the United States. And I think the question really is, how do we prevent this from happening next time?

And we really need to have a new system in place of corporate accountability and better tools and resources for FDA. We need the help of Congress to stop this from happening again.

Mr. DINGELL. We are trying to find out, first of all, whether you are protecting the American public. It's pretty clear, on the basis just of the questions, that you're not.

Now, I'm a friend of Food and Drug. I want you to have the authority to do what you have to do. I want you to have the pay and the personnel and the financial resources that it takes. I want to see to it that you have the capability in terms of procuring the cooperation that you need from importers and others. I want to be able to see to it that you could assure that manufacturers in China meet the same requirements for good manufacturing practices that Food and Drug imposes by statute on American manufacturers.

You cannot tell me that you are able to do that in China. You don't have enough people. You don't investigate them often enough. You haven't been able to stop the importers from bringing this in without the agreements that they're going to provide the necessary inspections in China. American manufacturers have to engage in manufacturing using, quote, "good manufacturing practices," closed quote; Chinese don't.

How does this situation protect the American public?

Dr. WOODCOCK. For heparin, we're stopping it at the border——

Mr. DINGELL. Not all of it.

Dr. WOODCOCK [continuing]. Unless we have an agreement with the——

Mr. DINGELL. You see, you've told me enough. Eighty-one people have been killed; hundreds have been made sick. It is not only in this country that people have been made sick or killed; it is in other countries around the world.

You are imposing constraints only, in a real sense, on a few of them. And that's only by voluntary agreement with the manufacturer and not by actually foreclosing these goods from being imported until you have an agreement which ensures that the American importer will properly inspect the plant which manufactures this stuff, which has, as you might well know, killed a fair number of Americans.

Dr. WOODCOCK. We must also remember that this is an essential drug, and we can't simply stop the heparin supply until we have put every single thing in place. We have to balance between access to heparin and our care in——

Mr. DINGELL. In other words, you want to balance between killing people and not killing people, as opposed to a balance between seeing to it that the laws are properly enforced and people can't be killed. Isn't that right?

Why can you not mandate these inspections in China in order to protect the American public? Do you have a statutory bar, a financial bar? What do you have that causes you all this pain and trouble?

Ms. AUTOR. If I understand the question correctly, sir, you're asking why we don't mandate manufacturers to inspect their suppliers. That is not currently the system we have in place. That is a system that I think we should move to, where everybody in the supply chain is responsible for ensuring the integrity and the quality of the components coming to them. That is not historically the system we have had. The best way to ensure that we get that system in quickly is to change the laws.

Mr. DINGELL. Why can't you just say to these importers, "You don't test, you don't bring it in"? Is there a bar to you doing that?

Dr. WOODCOCK. Well, testing, that is essentially what we are doing. We're saying unless——

Mr. DINGELL. But you're not doing it. You've already told me that you're not compelling them all to test. Some of them have not agreed to do so, and so some of them are not doing so.

Mr. Chairman, I find Food and Drug to be the most trusting institution in the world. You folks are more trusting than a kindergarten class.

Ms. AUTOR. I do not believe, sir, that I would be able to put all heparin coming into the United States on import alert. I do not believe that that would be——

Mr. DINGELL. I would be embarrassed, Mr. Chairman, to come up here and testify this way.

I yield back the balance of my time.

Mr. STUPAK. I thank the gentleman.

Mr. Burgess, for questions, please.

Mr. BURGESS. Thank you, Mr. Chairman.

A lot of questions are unanswered. Let me just be sure that I understand a couple of things now.

To voluntarily test all Chinese imports, you said that's not occurring at the present time, in response to one of the Chairman's questions. But all heparin coming into this country is being tested. Those companies are not doing voluntary testing. You referenced some of the compounding practices are perhaps not under voluntary testing. But all heparin coming into this country is currently being tested. Is that correct?

Ms. AUTOR. Yes, I believe that to be true.

Mr. BURGESS. Why don't we just stop heparin active ingredient from coming in from other countries?

Ms. AUTOR. There are two reasons.

One, I think we need to be concerned about potentially causing a shortage of a medically necessary drug.

Two——

Mr. BURGESS. Now, would that be important for this committee to consider?

Ms. AUTOR. Absolutely.

And, two, under our current legal scheme, I do not believe we have the authority to stop all heparin that's coming in at the border.

What we should have is a system where it's incumbent upon the manufacturers to show to us that their products meet FDA requirements, that they have approval, that they have the quality and the integrity and the safety necessary to come in. That's not currently the system we have in place, sir.

Mr. BURGESS. Well, it's pretty difficult, at least as I try to put this all together, with as many foreign manufacturers as we have far-flung across the globe and the people that you have to do the inspections. But we certainly can drill down on the points of entry into this country.

And that, to me, really seems to be where the rubber meets the road on this. Yes, we should have manufacturers that do their due diligence in the field, as we heard, I think, you testify to just a few moments ago.

Now, I actually heard Mr. Nelson say that—what did he tell us—that corporate due diligence cannot be relied upon. So there's a little disconnect between what you said and what he said.

But giving you the benefit of the doubt, at this point, manufacturers cannot assume that the FDA is going to do their quality control for them. Is that correct?

Ms. AUTOR. That is correct.

Mr. BURGESS. Manufacturers have an obligation to do that themselves. Is that not correct?

Ms. AUTOR. They do. And we should be holding them accountable.

And I think you raise a very important point. Right now, at the border, our authorities are 70 years old. We have to show that there appears to be something wrong with a product in order to keep it out. With drug import lines growing from 142,000 in 2002, of drugs, to 312,000 in 2007, to expect FDA at every one of those 312,000 circumstances, with probably 30 seconds to look, to be able to show that there's something wrong with the drug is not realistic. We need a system where it's incumbent upon the manufacturers to show there's something right about their drug before it comes into this country.

Mr. BURGESS. But even with that documentation and that verification, still the FDA is going to have to do the testing at the point of entry. And you have to have the ability to stop something dead in its tracks from coming into this country. Do you have that now?

Ms. AUTOR. In certain circumstances, we do. It's not about testing. It's about making sure that those requirements are met. And we do need to have that authority. We should be able to hold these companies accountable. We can do some of that, but we could do more with better tools and resources.

Mr. BURGESS. But with testing, with heparin, with recognizing what was happening—and then we heard testimony over the previous panel that tests would cost 1.7 cents per dose. So that seems to me something we should just be doing now with heparin, because we know there are people out there that are dishonest, we know they have a stealthy way to adulterate the product, and we know that people can die as a consequence because of the testimony you heard from our previous panel and because of the New England Journal of Medicine study that just recently came up and was part of the informational packet that was handed out.

We know all these things to be true. So heparin ought to really be subject to that additional, whatever it is, the testing, the microcapillary electrophoresis or whatever was done to document the safety of the product. That should just be a given now.

Dr. WOODCOCK. Yes. We got together with the international pharmacopeias, who are the international bodies that set testing standards for drugs that move in commerce.

Mr. BURGESS. These are the folks who had the test that didn't work before?

Dr. WOODCOCK. Yes. The USP and the European pharmacopeia. And so they have agreed to, on an expedited basis, put in new testing based on the FDA-developed test that would then be required to screen the products worldwide.

Mr. BURGESS. Now, let me ask another question that Mr. Shimkus brought up. Surfactant, does that mean—is the active ingredient surfactant being imported from overseas? I'm not sure I heard that correctly. Does anyone know the answer to that?

Dr. WOODCOCK. I don't know where it's imported from. I once knew, but I cannot remember the answer. We can get back to you with that.

Mr. BURGESS. Well, I guess the question I've got in my mind is, we have this new test for heparin, and we're going to be pretty certain that our heparin supplies are now safe. But what's next?

Who is thinking like a criminal and trying to develop the next model—the melamine, the ethylene glycol, now the hypersulfated chondroitin sulfate? Is there any computer modeling that anyone is looking at to try to discern the next level of thuggery that's going to come across our borders from the People's Republic of China, not to mention any particular country?

Dr. WOODCOCK. That's a level of sophistication and information management that we don't have right now. We need to get a grip on the basic inventory of firms and their unique identifiers.

And then that's another thing. What you're alluding to, that sort of general intelligence about what's going on there with the drug supply and the sources is something we would like to also develop.

Mr. BURGESS. I mean, I don't know how this happened, but you've got a patent there in China from 2005, and now 2 years later we're looking at this problem. When someone put all of this together, some clever scientific mind who also happened to be not just devious but deadly, I just think there's got to be some way we've got to be able to try to anticipate these things before they happen.

Because, otherwise, you're looking at an adverse event reporting system that we heard from the dialysis nurse is not—it's hard to aggregate that data and get it in a place where it's going to be meaningful. And we just heard testimony from the last panel that a month goes by and we lose two individuals from one family. I mean, that's a pretty harsh reality to have to accept.

So is there a way to be more proactive about this and try to figure out where the next threat is coming from?

Ms. AUTOR. Sir, I agree with you, it's a tragic situation. And I believe, with respect to the systems and the threat analysis that you're talking about, I would love to get there. I think we're a long away from there.

I think there are a lot of things we can put in place in the interim which would go a long way toward trying to prevent this kind of problem. I think having pedigree for products, having good distribution in importer practices, having testing for impurities, having modern manufacturing signs—all of those things are things which will help to ensure the quality and integrity of the drug products.

It may never be possible to anticipate all kinds of thuggery, but we can put a system in place that's looking for it, where the manufacturers are looking for it, the suppliers are looking for it, the importers, the brokers are all looking for it, and FDA is holding them accountable and also looking for it. And that's where we need to go.

Mr. BURGESS. Well, one of our jobs here in Congress, of course, is to defend the borders. And this, to me, is fundamental border defense. And it is one of the things that we ought to be paying for, one of the things that Congress ought to fund.

We've heard a lot of discussion about the President's budget. What is the dollar amount that was given to the FDA in the recently passed House budget? I realize the House and Senate have not come to a unified budget resolution. The President's number is well-publicized and well-criticized. What is the House number?

Dr. WOODCOCK. I don't know the answer to that. I'm sorry. You mean particularly for pharmaceuticals?

Mr. BURGESS. Well, for the FDA overall. We were talking about the budget increases under the President's budget didn't do nearly enough. And we've heard other figures bandied about today.

What was the figure that we put to the FDA as a result of our budget discussions this year?

Dr. WOODCOCK. I don't know the answer.

Mr. BURGESS. That's a problem. I don't know the answer either. And I've had several good minds working on this for a couple of days, and they can't find the answer either. So, apparently, in the most transparent Congress in American history, we don't know the amount of money that we budgeted last month for the Food and Drug Administration.

And that's a problem in my mind, that we're willing to criticize the work that you do, we're willing to criticize the White House for coming up with a budget, but the reality is we can't even tell from our own budget what we're going to give you next year.

That's assuming we even get to the point where we do Labor-HHS appropriations, which, quite frankly, I'm pessimistic that we'll see that happen.

Let me just ask one last question. We're going to be involved and embroiled in the whole debate over biosimilars here in just a very short period of time. What are the implications for the generic biologics or the biosimilar, the bioidentical drugs, what are the implications for that debate from what we've learned about the heparin issue?

Dr. WOODCOCK. I'm fairly expert in this area. I can tell you that the production of the recombinant products, which most of the biosimilars are, or are being contemplated to be, is very tightly controlled. And, ordinarily, API——

Mr. BURGESS. But not in China.

Dr. WOODCOCK. In China, as well. China has very little recombinant fermentation that they're engaging in now, but I'm sure they're interested in getting into that.

Mr. BURGESS. They certainly are. And if the money is there, I'll bet they follow the money.

Now, how are we going to protect ourselves if this same larcenous individual, who has yet to be identified, who slipped this stealth product into the heparin, how are we going to protect ourselves with the bioidenticals that we're now charging down the road to approve?

Dr. WOODCOCK. I think what we have to say is that we need a safety net that includes more frequent inspections, protections at the border, so that we know what the inventory is and we don't let things in unless they are affirmatively okay. We need the best possible science. And we need the IT systems to support all that and track these.

And those tools for FDA then could be used to hold the manufacturers accountable. That's a principle of quality management, is that the supply chain in every step of the manufacturing maintains that quality. We can do that, FDA can do that, if we have the tools.

Mr. BURGESS. But we didn't do it with respect to the active pharmaceutical ingredient for heparin.

Now, let me just ask you this one last question. Are we ever going to get to the point where we have a synthetic heparin and we don't have to rely on animal sources?

Dr. WOODCOCK. Yes, there certainly are alternatives on the market now to heparin for some indications. And there are certainly individuals or firms that are interested in developing synthetic versions.

However, of course, there's a cost differential, and there's a great interest in the country in holding down health-care costs and keeping affordable drugs on the market. And these two things are a tension.

Mr. BURGESS. Thank you.

I'll yield back, Mr. Chairman.

Mr. BURGESS. Thank you.

I yield back, Mr. Chairman.

Mr. STUPAK. I thank the gentleman.

Ms. Schakowsky, for questions, please.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

Ms. Brown, I would like to ask you a few questions.

From February 20th of this year to February 26th, you were the investigator on an FDA team who inspected the Chinese plant, actually went there, known as Changzhou.

After all this time, I'm still wondering how to pronounce it. Is it Changzhou?

Changzhou SPL, which supplied the purported tainted heparin. Is that correct?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And your inspection of Changzhou SPL revealed significant deviations from U.S. current good manufacturing practices. Isn't that correct?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And I would like to ask you some questions about this inspection and your findings.

First, isn't it true that you found that Changzhou SPL's processing steps provided no assurance that they were capable of removing impurities?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And isn't it also true that you found that Changzhou SPL failed to have adequate systems for evaluating both the crude heparin and the suppliers of crude heparin to ensure that the product was acceptable for use?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And, in fact, didn't you find that the Changzhou SPL received crude heparin material from an unacceptable workshop that was used to manufacture heparin, manufacture heparin API, and that this API was imported into the United States?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And you also found that Changzhou SPL failed to ensure raw materials were of an acceptable identity, quality, and purity before use. Isn't that correct?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. Now, can you tell us why understanding the origin, quality and purity of these materials are essential for meeting good manufacturing practices, particularly when you're making a biologic such as heparin?

Ms. BROWN. In particular for heparin, the certificate of analysis that came with the crude material into Changzhou SPL was the only source identifying it as crude heparin from a porcine source.

Ms. SCHAKOWSKY. From a——

Ms. BROWN. From pigs.

Ms. SCHAKOWSKY. I see. And why is that important, the fact that that was the only document?

Ms. BROWN. Because Changzhou SPL actually had just begun PCR testing, which verified the pig origin of the crude heparin in June or July of 2007. So it was a relatively new test that they were doing. Prior to that, they hadn't done it at all in China.

Ms. SCHAKOWSKY. I see. Didn't you find that the test methods performed by Changzhou SPL had not been verified to ensure suitability under actual conditions of use? Is that what you're saying, that it was unverified?

Ms. BROWN. Yes, unverified. The tests that they ran were USP compendial methods, and we ask firms to verify that the methods are suitable for use with their particular product.

Ms. SCHAKOWSKY. I see. So what does it mean when the FDA says that Changzhou SPL's test method had not been verified to ensure suitability under actual conditions of use, and why is this important?

Ms. BROWN. Well, one of the tests that they ran was a protein test that was a turbidity test. They put a required solution in a big test tube and then added their substance to it. And if turbidity showed up, then the crude heparin did not have protein in it. And if it didn't show up, then there was protein there. Or—I think it was the opposite. If it got turbid, there was protein in it. So it's kind of a crude test.

And the first steps of the purification process for heparin involves getting rid of protein. So they tried to do process validation, and they used this turbidity test in the process validation too, and they never showed that it was repeatable.

Ms. SCHAKOWSKY. OK.

Ms. BROWN. So it may not have been suitable for use as an in-process test and even as a finished product test.

Ms. SCHAKOWSKY. And you reported that?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. You found that the equipment SPL used to manufacture heparin was unsuitable for its intended use. Isn't that correct?

Ms. BROWN. Yes.

Ms. SCHAKOWSKY. And how was it unsuitable? And why is this important?

Ms. BROWN. There were three different pieces of equipment that I found unsuitable for use.

The first one was these big polyethylene tanks that they dissolved heparin up in just prior to the last manufacturing step, which was a lyophilization—a freeze-drying step. And these PE tanks were scratched on the bottom, very scratched, as though somebody had been chopping stuff out of them with plastic. Like, I could—I ran my fingernail along it. It was like playing an accordion. And there was also stuff adhering to the bottom of these tanks, and they were marked——

Ms. SCHAKOWSKY. This is inside the tanks?

Ms. BROWN. This is on the inside of the tanks where crude heparin would be right before it became the API, right? So I scratched stuff off the inside of the tank. And this was a tank that was marked clean.

A second PE tank I turned over and liquid fell out of the handles, the molded, PE, it comes from a mold, polyethylene—and a liquid fell out of the handles into the bottom of the tank. And it was marked clean. So it wasn't a clean tank.

Ms. SCHAKOWSKY. "Stuff." Do we know what stuff was in there?

Ms. BROWN. The stuff I scratched off? No, I don't know what it was. It was a little gray-colored. It wasn't white, is all I know.

Another piece of equipment was the centrifuges that they used to get rid of the waste protein. They used two of them. They had one that would be in use, and then they'd clean the sludge out of the other one while—to find out how long they should run the one that was going, like, will it last 30 minutes without getting too full? And that was a very unusual manufacturing step. It wasn't described in the procedures for how to use the centrifuges. So you had to actually be at the plant to figure out what they were doing. Normally, you see one centrifuge and you run your material through it and separate the solid from the liquid.

The third piece of equipment that was a little—that was outstanding to me was their lyophilizer. They didn't have the software that would provide for the person running it, for the parameters that he put——

Ms. SCHAKOWSKY. What is that?

Ms. BROWN. Oh, the lyophilizer is the big freeze-dryer. So you put in these trays of liquid, and they turn into solid after days, sometimes. You freeze the liquid, and then you warm it up slowly, and they're under vacuum, so it turns into a solid material.

All right. So for this lyophilizer, there were no records of the actual parameters that were punched into the screen at the front of it—but there was no screen at the front of it. There was no way to tell what temperatures they actually used to dry the material.

Ms. SCHAKOWSKY. So this is clearly substandard or not up to par on what it should be?

Ms. BROWN. Yes. The settings weren't there.

Ms. SCHAKOWSKY. They just weren't there.

Why couldn't Baxter's audit have found these things, do you think?

Ms. BROWN. I don't know. I walked through facilities as part of my inspection. I don't know if they did that.

Ms. SCHAKOWSKY. In your book, if you would—do you have it?

OK. If you could hand that to her.

It says 18, which is Exhibit 18 in the exhibit book.

Ms. BROWN. OK.

Ms. SCHAKOWSKY. OK. Item F of that EIR states the following: "there was no person with special knowledge of heparin at the firm to guide decisions made by the quality unit."

So, Ms. Brown, I would assume that if a plant was making heparin API, it would want to have a person with, quote, "special knowledge," unquote, of that product in case deviations from any manufacturing process were observed. Wouldn't you agree?

Ms. BROWN. I think it's—they had a quality unit there, which consisted, I believe, of four people. And they were trying to track what was going on at the firm.

The person with the special knowledge I mentioned because, when I arrived, management was aware that there were Baxter recalls and that there were adverse drug events and deaths in the United States. It was middle of February. And the general manager of the firm, Mr. Wang, was the one who described the process to me and the process of how he thought that impure materials were removed from the crude heparin to make it into the heparin API. And he said he wasn't a heparin expert.

And so, he was really the person who gave me my fullest extent of knowledge during the inspection.

Ms. SCHAKOWSKY. So neither he nor the others had any special knowledge. He had the most knowledge, you're saying?

Ms. BROWN. I believe so. Yes.

Ms. SCHAKOWSKY. OK. Thank you very much. I think I've run out of time. I appreciate your answers.

Ms. BROWN. Thank you.

Mr. STUPAK. All right. Just a couple of follow-up questions, if I may.

Ms. Brown, I want to thank you for your thorough inspection of this Changzhou facility. I couldn't help but notice that, during the testimony of our first panel, especially the family members, you were touched by that. And I could see that it brought home to you the importance of the work you do day-in and day-out and many of the employees at the FDA. So we thank you.

Let me ask you this question, Ms. Autor. You said, we should hold them responsible, being Baxter, in response to a question put by Mr. Burgess.

Now, this plant was never inspected in China by the FDA. Is that a violation of the law, to send active pharmaceutical ingredients from a plant that's never been inspected for sale here in the United States?

Ms. AUTOR. Well, I'm not a lawyer for the agency, so you could ask them. But my understanding is that is not a violation, no.

Mr. STUPAK. It is not a violation.

Ms. AUTOR. No. No. But obviously, the law could be changed to allow that and to give FDA, for example, the authority to require a recall. Right now, we can't even require a recall if there is a product in commerce that we believe is dangerous. We can only ask.

Mr. STUPAK. Can you tell me the last time the FDA asked for recall authority?

Ms. AUTOR. I cannot offhand, but I can tell you right now that I think it is something that would be very helpful to the agency.

We have it for devices; we don't have mandatory recall authority for drugs.

Mr. STUPAK. Dr. Woodcock, has FDA ever asked for recall authority?

Dr. WOODCOCK. I don't know.

Mr. STUPAK. I can tell you the answer right now. I have been here for 12 years. And the answer is no, you have never asked for it.

Dr. WOODCOCK. I do not know.

Mr. STUPAK. OK. Let me ask you this: is it a violation of the law to ship a product from China from a plant that has not been approved to the United States? Do you know that?

Dr. WOODCOCK. My understanding is, as Ms. Autor said, is it is not a violation of the law.

Mr. STUPAK. OK. So for Baxter having them send products to the United States from a plant that was never inspected by the FDA, there's no penalty the FDA can assess to them? There's no fines, no costs, no nothing, right?

Dr. WOODCOCK. That's my understanding.

Ms. AUTOR. And we don't actually have civil money penalty authority for drugs at the moment.

Mr. STUPAK. I realize that. I realize that. Would you like that authority?

Ms. AUTOR. I would.

Mr. STUPAK. Would you? OK, good.

Let me ask you this, some questions Mr. Dingell asked. And it's my understanding, currently the burden of proof is on the FDA to document that a drug is unsafe. Is that correct?

Dr. WOODCOCK. Yes.

Ms. AUTOR. The burden is that we must show that it appears to be adulterated or misbranded or unapproved.

Mr. STUPAK. OK. So wouldn't it make the FDA's job of protecting Americans a lot easier if foreign firms had the burden to prove that their drugs are safe before they ever could be shipped to the United States?

Ms. AUTOR. Absolutely.

Dr. WOODCOCK. Yes.

Mr. STUPAK. OK. Is that authority you're going to ask for?

Ms. AUTOR. I cannot speak to what the agency will officially ask for. As somebody who does this day-in and day-out, I can tell you that would be a very useful tool.

Mr. STUPAK. Would you agree with that, Dr. Woodcock?

Dr. WOODCOCK. Yes.

Mr. STUPAK. Is that authority you would ask for, as head of the Center for Drug Evaluation and Research? You evaluate these drugs, so it would be your department that would have to make that determination. Is that authority you would ask for?

Dr. WOODCOCK. Again, we don't ask for authorities directly. This would be a tool that the Center for Drug Evaluation and Research would find very helpful.

Mr. STUPAK. You're right. You don't ask for authority directly, you just said. And so, how do you work with Congress then, if you never ask us for the authority? If you're supposed to be the expert, how are the Members of Congress supposed to know, if you never ask for the authority?

Dr. WOODCOCK. Well, we are providing you with this input right now, that we feel this would be a very useful authority, along with civil money penalties, the ability to stop products at the border and not let them in, mandatory recalls and so forth.

Mr. STUPAK. How about subpoena power? Would you like subpoena power?

Ms. AUTOR. I think that would be very useful.

Mr. STUPAK. Dr. Woodcock?

Dr. WOODCOCK. I agree with that. Yes.

Mr. STUPAK. Hallelujah. I asked you that a few years ago; you said, no, you didn't need it. I'll bring back the testimony, just so you know. We're making progress. We're making progress.

Let me ask you this question. Go to Exhibit No. 20, if you would, Dr. Woodcock, in the exhibit book. Exhibit No. 20.

OK. Now, in your heparin investigation, this is—you've got Exhibit No. 20. It's a 3-page report here.

Dr. WOODCOCK. I have an establishment inspection report, tab 20.

Mr. STUPAK. OK. Now, were you able to make this inspection of this—consolidators for heparin, correct?

Dr. WOODCOCK. Is this Hangzhou?

Mr. STUPAK. Yes.

Dr. WOODCOCK. Yes. Yes.

Mr. STUPAK. OK. Now, there were two, and you were able to make this—there were two consolidators. Were you able to inspect the other consolidator?

Ms. AUTOR. I think Ms. Brown could best talk about what happened in China.

Mr. STUPAK. Ms. Brown?

Ms. BROWN. Yes, I inspected both.

Mr. STUPAK. Did you have any trouble obtaining the information or going through these plants, getting the information you requested?

Ms. BROWN. Yes, I had a little trouble at both of them.

Mr. STUPAK. At both of them. In what way? What would the trouble be? In gathering information? Allowing us to see things? Explain that.

Ms. BROWN. At Changzhou Techpool, we had no trouble accessing records or walking through the facility, but we couldn't copy—get copies of any of the records that we had looked at.

Mr. STUPAK. OK.

Ms. BROWN. That is the first one.

At Hangzhou we were able to walk through, but we were not able—that was only on one day. The next day, we were refused further walks through the lab, which we hadn't walked through.

Mr. STUPAK. But a lab would be critical, would it not, to determine what happened?

Ms. BROWN. Yes. And we were refused access to all records. And I think, as I recall, the president of the firm didn't want to answer any more questions about the—that would be like an inspection.

Mr. STUPAK. OK. Well, Dr. Woodcock, you mentioned in your testimony this international agreement that you have with China, a memorandum of agreement. Dr. von Eschenbach mentioned it last week when we were talking about heparin when he was here.

So how does this agreement help, if you can't go to the lab, they won't answer your questions, and you can't make copies of records? How does that help us be safer and do our inspections that are required?

Dr. WOODCOCK. Well, obviously, we need the ability to do those things for any supplier. And we need the ability to not accept the API, whatever it might be, if we have not been able to do the inspection.

And Debbie might say more about the agreement.

Ms. AUTOR. I believe the memorandum of agreement with China was useful in that it helped us to expedite these inspections. We were able to get to Changzhou SPL, for example, in something like 5 days, which is relatively unprecedented. And it helps by establishing opening lines of communication between us and the Chinese regulators. But——

Mr. STUPAK. But it doesn't help you to get in the labs, doesn't allow you to make copies, doesn't allow you to talk to the employees.

Ms. AUTOR. It does not. It does not.

Mr. STUPAK. So you get to the country a little faster and you can see where the place is located, and that's about it, right?

Ms. AUTOR. The agreement is a start, but it is not the answer to all Chinese drug quality issues. That's correct, sir.

Mr. STUPAK. Well, Ms. Autor, isn't it really true that—because Baxter's audits found this plant to be satisfactory, had it not been for the heparin crisis, the subsequent FDA inspection of this plant would likely be shipping drug product into the United States?

In other words, you wouldn't have known this plant was operating out of compliance without good manufacturing practices, had it not been for the crisis, in the physical inspection, right?

Ms. AUTOR. I'm not sure I follow the question, sir. I'm sorry.

Mr. STUPAK. All right. You would have never known that this plant was even operating, without this heparin situation, right?

Ms. AUTOR. But for the heparin situation, this firm would have been considered for inspection on an annual basis, along with the other——

Mr. STUPAK. Thirty or 40 years from now.

Ms. AUTOR. It would be put in the list of roughly 3,300 facilities that are ranked. And I can't say exactly with application of our risk model whether or when this would have come up for inspection. And, again——

Mr. STUPAK. If you receive from a manufacturer a certificate—did you receive a manufacturer's certificate here from Baxter that this plant was manufacturing heparin and that it passed their inspection? Would the FDA have received that information?

Ms. AUTOR. No, sir, probably not.

Mr. STUPAK. That's for Baxter's internal use, then, right?

Ms. AUTOR. Yes.

Mr. STUPAK. How do you become aware, then, of a plant that is manufacturing and is going to ship a product, an API, an active pharmaceutical ingredient, to the United States, how do you become aware of it? How does the FDA become aware of it?

Ms. AUTOR. Well, there is our registration and listing system, and there also is a system at the border where we keep a count of who is coming——

Mr. STUPAK. What is the sanction if people don't register with the FDA?

Ms. AUTOR. If a foreign facility is not registered and not listed, if it's not listed, its product would be considered to be misbranded. And, at this point——

Mr. STUPAK. But how do you know that? I mean, if someone doesn't tell you, we're starting up this plant in Changzhou, China, how do you know? You don't know, do you?

Ms. AUTOR. We would know at the border that they're bringing a drug in, that's correct.

Mr. STUPAK. OK.

Dr. WOODCOCK. In addition, for most products in the United States, just to be clear, that are approved products, they must submit an application for the particular plant, a manufacturing supplement to allow that plant to be used, the material from that plant to be used as an ingredient in the finished drug product.

That's not true for monograph products. It's not true for compounding. And so there are a few other instances where that is not the case, and we have to rely on registration and listing.

Mr. STUPAK. But, really, without an inspection, you don't know what a plant's producing, right?

Dr. WOODCOCK. That's right. And that's why we try to go to—for pre-approval inspections to plants. This was an error that we did not visit this plant the first time.

Mr. STUPAK. And we don't know if a plant is meeting the good manufacturing practices unless it's inspected?

Dr. WOODCOCK. That's correct.

Mr. STUPAK. Do you know how many plants are out there that have not been inspected?

Ms. AUTOR. I imagine there are a quite a few. The number of foreign sites making FDA-regulated drugs in 2001 was about 1,200. In 2007, it was about 3,000. And our number of drug inspections has actually declined from 2001 to 2008.

Mr. STUPAK. And your IT information, OASIS, says it could be as high as 7,000, correct?

Ms. AUTOR. I would rely on the drug registration listing and not on OASIS for that number, sir.

Mr. STUPAK. Really? Why do you have two sets of numbers then?

Ms. AUTOR. We certainly need to improve our IT systems, and we're working to do so, absolutely.

Mr. STUPAK. I've been hearing that since 1998.

Mr. Shimkus, questions?

Mr. SHIMKUS. Thank you, Mr. Chairman. I just have a brief one.

The question is after—Ms. Brown, we appreciate your inspection. So you go, and you inspect, and you give a report, and that report goes to the administration.

And it's kind of an intro to you, but response to Dr. Woodcock or Ms. Autor, or whoever's the best answer.

When would we expect that FDA inspector to return to that facility? Does anyone know?

Ms. BROWN. I would only return if I got an assignment.

Mr. SHIMKUS. OK.

Ms. AUTOR. How soon would we return? I'm sorry——

Mr. SHIMKUS. There's a lot of identified problems with this facility. What triggers our return?

Ms. AUTOR. I expect at this point that the company will respond to our warning letter in writing, and we will go back and verify any corrective actions that they've undertaken before we consider this issue to be resolved.

So I think it would probably be within the space of about a year, depending on where they respond and how they've responded. But that's a guess.

Mr. SHIMKUS. So if the company then writes in a response and ends up saying, "We've corrected all these deficiencies," what's the timeliness of a return inspection?

Ms. AUTOR. We would go back—we'd have to look at the response and see how adequate it was. If we got to a point where we felt there had been an adequate written response, then we would make it a priority to go back there. But it could be a matter of months, it could be a matter of years, depending on the response.

Mr. SHIMKUS. If it was an inadequate written response, you would go back?

Ms. AUTOR. No, if it was adequate. Remember, at this point——

Mr. SHIMKUS. But if it is an inadequate response——

Ms. AUTOR. Then we would tell them it's inadequate. At this point, they're not allowed to ship products into the United States. So how quickly we will go back there will depend on when we think these issues might be resolvable and they may be allowed to ship——

Mr. SHIMKUS. And have we ever reauthorized facilities to ship again with an adequate written response without a follow-up inspection?

Ms. AUTOR. Not when there's an import alert. We would go back for an inspection.

Mr. SHIMKUS. Say that again?

Ms. AUTOR. If there is an import alert, as there is here, where all the company's products are detained at the border without physical examination, we would go back and verify that the corrective actions are adequate and have been adequately implemented before we lifted that import alert.

Mr. SHIMKUS. You used a terminology that there is a risk model. Is there a risk model?

Ms. AUTOR. There is a risk model, sir, which involves taking the foreign inventory and we run it through our domestic risk model, which means we rank the facilities based on risk presented by the product, process, and facility. And we then, from there, look at other factors, like when the facility was last inspected, when they shipped to the United States, and various other things. And we use that to rank our foreign facilities for inspection.

However, given the fact that we have roughly 3,300 foreign facilities, we rank about 100. And then we end up inspecting, say, 300 or so. It doesn't—I would not tell you that that risk model therefore means that we have covered all high-risk foreign facilities.

Mr. SHIMKUS. And then I want to end up on just—since we have you here, and Members do this every now and then. How does this whole debate about our processes, and with a pharmaceutical company that we know of and we have these problems, how does this affect our ability to know the safety and efficacies of drugs that are reimported?

Ms. AUTOR. You are talking about personal importation?

Mr. SHIMKUS. Yes.

Ms. AUTOR. I believe that that also raises public health concerns, because we do not know where those products come from. We do not know the conditions under which they were manufactured. We do not know the conditions under which they were stored or their labelling. Another issue where there are quality concerns.

Mr. SHIMKUS. There is really no trail there?

Ms. AUTOR. Correct. Correct. And even at this point, we do not have pedigree for drugs coming into this country. And that would be very useful, as well as the ability to inspect importers and to prohibit sale of drugs, for example, that weren't declared as drugs when they were imported.

Mr. SHIMKUS. Yes. And I know that's something that, in previous Congresses, this committee itself had done a lot of good work on reimportation.

I'm just going to yield the rest of my time to Dr. Burgess.

Mr. BURGESS. Thank you. I appreciate the gentleman yielding.

When we had our food safety hearings earlier this year, the comparison with FDA and USDA on the concept of equivalence—the United States Department of Agriculture requires the facilities, although they're in a different country and they may do things differently, that they be equivalent to the standards that we have in this country—and we learned that there is no standard of equivalence for imported food from the jurisdiction of the FDA.

Does this concept of equivalence apply to the active pharmaceutical ingredients that are imported?

Dr. WOODCOCK. Yes, it applies. We would require these to meet U.S. standards. It is more about our ability to find them, track them, keep them out and hold the manufacturers accountable. Because we don't have the reach, as we have said, and we don't have the tools, the authorities, to do this as effectively with this flood of imported drugs coming into the country. But they are supposed to be to our standards—to meet our standards.

Mr. BURGESS. When you say "authority," do you lack the authority in a foreign country to go in and make the demands that it be equivalent to United States manufacturer?

Ms. AUTOR. We do not have the authority to demand entrance to a foreign facility. We do have the authority to keep things out of the country that appear not to comply with our standards.

Mr. BURGESS. Now, when we had—and it may be a little bit of a different jurisdiction, but certainly with food safety and certainly as applied to the Consumer Product Safety Commission, which is obviously a different agency but still some of the same concepts apply, it seems like we've been told at several different junctures that we can't keep things out because of trade agreements, that that then becomes an issue for international trade.

Has that become an issue for the active pharmaceutical ingredients?

Ms. AUTOR. I'm not a trade expert. I think there are concerns raised with respect to putting different burdens on foreign commerce than on domestic commerce. But I think——

Mr. BURGESS. Has that been at all an impediment toward getting the absolute import ban that you were after?

Ms. AUTOR. I think, at this point, the biggest impediment is the standard in our law which requires us to show an appearance of a violation. And that's a difficult hurdle to overcome. But I think that if we can meet that burden, then I have not heard trade concerns raised at that point.

But, again, if it were incumbent upon the manufacturers to show us that their products should come in, then that would be a much easier burden on the agency and a much better way——

Mr. BURGESS. Can you state that again for me?

Ms. AUTOR. Yes. If it were incumbent on the manufacturers or the importers to show us that their product meets FDA requirements before they are allowed to come into this country, then that would be a much tighter net and a much better way of ensuring the safety and integrity of the American drug supply.

At this point, it is incumbent upon the FDA. And, for example, if we have not been into a facility, we can't keep the product out just because we haven't been there. And at this point, there are a lot of facilities, as we said, that we have not been in.

Mr. BURGESS. What prevents you from having that higher standard, tighter net, that you just described?

Ms. AUTOR. Well, the standard in the law is the same one it's been since 1938. It talks about an appearance of a violation, which is really based on, I think, historically, looking at the product and seeing if there is something wrong with it, and obviously that's an antiquated concept.

Mr. BURGESS. Yes, it would seem so. And I guess I'm having trouble with the fact that it hasn't been looked at, addressed. I mean, Mr. Stupak has been here for 12 years, 14 years. He hasn't fixed it yet after all this time?

Mr. STUPAK. I'm in the majority now. I'm going to get to it, Mike.

Mr. BURGESS. When? When? You've been in the majority for 14 months. I mean, it's time, Mr. Chairman.

Ms. AUTOR. I think if you look at the history of food and drug law, sir, you will see that it is often a crisis that compels change. And it is often not until a crisis that a change is made. But I would submit that we currently have a crisis and an opportunity to make real change.

Mr. BURGESS. I would agree with that observation.

Now, do you think that your inability—or the fact that you had to demonstrate that the product was harmful before you could issue the import ban, did that in any way interfere with the product recall that was going on in this country? Did that slow things down?

Ms. AUTOR. I think that we have been able to, on a rapid basis, put in the necessary safety net with respect to heparin. It would be a little easier if we were able to put in an import alert for all heparin and say, you have to show us the test results before the product comes in. I do not believe we currently have the authority to do that. But, again, I believe that we put in an adequate safety net promptly with respect to all imported heparin.

Mr. BURGESS. Of course the question probably should be asked to the manufacturer. But it seems like it would be in their enlightened self-interest not to allow a product into the country that would then be damaging to them just even from a publicity standpoint or the negative branding that would occur, or undoubtedly has occurred, because of this situation we find ourselves in now.

Dr. WOODCOCK. All the major manufacturers are doing testing. In fact, they voluntarily went back and looked at all their prior lots of API, back into 2006 and so forth.

What we're talking about, though, there are many smaller uses of heparin, smaller manufacturers and so forth, who may not have the capacity to test. So we're stopping all those, making sure we test them or they're tested before they get in.

Mr. BURGESS. I guess the point I'm trying to get at, though, is, was there anything in this restrictive standard that you have that's been in place since 1938 that delayed getting the appropriate recall done of the product? Was the manufacturer less likely to go forward with the recall because you had to comply with the 1938 law?

Ms. AUTOR. I would not say it delayed it. But because of the appearance standard, the burden is on the agency initially to do the sampling of the heparin and the testing of the heparin that's coming in. Whereas, if the burden were different, if it were the manufacturer's responsibility to show that their product complied with our requirements, then we could ask them to give us the data in the first place to let the products in.

With respect to the actual recall of products and interstate commerce, at this point I would not say there was particular resistance by the manufacturers to do the recalls or delay because of our authority. But, in my experience, there certainly have been situations where manufacturers have been reluctant to do recalls and they have been delayed because we did not have the authority to order those recalls.

Mr. BURGESS. But that was not the case with this product recall?

Ms. AUTOR. No, sir.

Mr. BURGESS. And in fact, when the dawning first started to occur that there was a problem, but perhaps the depth and the breadth of the problem was not anticipated, was there a concern that we were going to remove a product from the armamentarium that was very necessary for some medical therapies to continue?

Dr. WOODCOCK. Yes. And we have a shortage team and routinely in our operations have to look at, for medically necessary drugs, the balance between creating a shortage and losing lives, perhaps, because there's a shortage of an essential drug, versus a recall. And so we operated that, in this case, because this particular manufacturer's supplying about half the U.S. heparin supply, is my understanding, of this type of heparin, USP heparin for injection.

Mr. BURGESS. How long did it take before you, as an agency, were convinced that you had an alternative, a satisfactory alternative stream of product to meet the medical demands?

Dr. WOODCOCK. It didn't take us a very long time. We have a very, very good shortage team. I can't tell you exactly, because we were—the initial thought by the CDC, for example, was this was yet another problem with the dialysis tubing or the membranes and so forth. And so it took a while to sort out and then actually link it with Baxter.

And then it was felt perhaps it was just the large multi-dose vials, because those were the ones we got reports on. That was put into play. And then we got a bigger picture, the bigger picture that it might be associated with all of the heparin, the vials of heparin that Baxter was shipping.

Mr. BURGESS. Has the agency prepared a timeline as to when the first reports were coming in, when your involvement was, when Baxter's involvement was?

Dr. WOODCOCK. Yes.

Mr. BURGESS. Is that something you could make available to the committee?

Dr. WOODCOCK. Yes.

Mr. BURGESS. OK. I would appreciate that.

Mr. Chairman, I yield back the balance of my time.

Mr. STUPAK. I thank the gentleman.

Just a quick question. Now, the FDA will have to go back and reinspect this plant before it can ship heparin to the United States, correct?

Ms. AUTOR. Yes.

Mr. STUPAK. Who pays for that, the taxpayer or the manufacturer of the heparin?

Ms. AUTOR. The taxpayer pays for that. We do not have any authority to have anyone else pay for that, at this point, sir.

Mr. STUPAK. OK. When you go back to do the reinspections, is there any limitation on what you can inspect? Is it going to be just the plant? Or can you go back to the workshops where this heparin first originates, as you had indicated earlier it might be helpful to inspect those?

Ms. AUTOR. We can go back. I cannot say whether they will admit us or not, or whether they will allow us to do a full inspection. We can certainly go there and ask to inspect.

Mr. STUPAK. So it's still up to them whether or not you will be able to inspect the workshop or the consolidator or things like that.

Ms. AUTOR. Correct. In this country, if an inspection is refused, we can go to court and seek a warrant. We cannot do that in a foreign country.

Mr. STUPAK. OK.

Dr. Woodcock, you indicated a couple of times to Mr. Burgess and Mr. Shimkus that we should hold the drug manufacturers responsible. It seems to contradict the policy of the FDA.

Drug manufacturers must be held responsible for drug safety, you say. But how do you justify, then, the position of the Office of the Chief Counsel that companies making approved drugs, like Baxter, should not be held liable in State courts for injuries caused from drugs like heparin because it was approved by the FDA?

So how do we hold them responsible if you are going to give them immunity from prosecution for injuries because they were FDA-approved, even though we have adulterated drugs which, unfortunately, we have deaths associated with?

How do you justify that? It seems like a contradiction.

Dr. WOODCOCK. I was saying that we need to hold manufacturers accountable for the compliance and for quality throughout the entire supply chain.

As you know, I'm a physician. I'm not really qualified to comment on the liability issues.

Mr. STUPAK. But don't you see the contradiction there? Just because the FDA approves a drug doesn't necessarily mean that it's always going to be safe, does it? Because it can be adulterated, like heparin or melamine or DEG in toothpaste that we've seen before.

Dr. WOODCOCK. That's correct.

Mr. STUPAK. OK. I have nothing further.

Mr. Burgess?

Mr. BURGESS. If I could just clarify one point. Now, at this juncture, we can't say for certain if this contamination of the heparin was intentional or unintentional?

Dr. WOODCOCK. We have no evidence one way or the other.

Mr. BURGESS. Could I just ask under what plausible scenario it could be unintentional?

Dr. WOODCOCK. Through our chemical analysis and our collaborators, we were able to discern that this was chemically modified chondroitin sulfate.

Mr. BURGESS. Right.

Dr. WOODCOCK. And it is not—we have also done investigations and determined it really wouldn't be present in the pig, in the animal. So it wouldn't be an impurity that would have resulted from problems, say, in the purification process.

Mr. BURGESS. You are telling us it was intentional because it appeared in multiple manufacturing sites and in multiple locations?

Dr. WOODCOCK. That's certainly the highest probability.

Mr. BURGESS. And the pig didn't suddenly change genetically to start manufacturing this stuff in its gut. Someone put it in.

Dr. WOODCOCK. We looked into that, because possibly the viral disease that was in China or whatever might have altered the sulfation patterns of the chondroitin sulfate. And we have concluded that this is not a naturally occurring sulfation pattern.

Mr. BURGESS. I am reassured to know that. So no spontaneous generation of this stuff within the pig's intestine.

Dr. WOODCOCK. That's right.

Mr. BURGESS. So under what plausible scenario could it be unintentional?

Dr. WOODCOCK. Well, it is hard to determine how it could have been introduced accidentally. In some cases, as was said earlier, the contamination was up to 20, 30 percent or higher of the heparin. And that does strain one's credulity that it could have accidentally gotten into the crude heparin or API.

Mr. BURGESS. Several years ago, when the manufacturer of Tylenol in this country was faced with a situation where there was suddenly—I don't remember—arsenic that appeared in a Tylenol capsule, I mean, clearly that was an after-market addition, after they did the appropriate investigation.

So is it likely that we are going to find a similar situation here, that this is a Tylenol problem on just a much larger scale?

Dr. WOODCOCK. I don't know the limitations of our ability to determine the root cause of this. I would defer to Deb Autor about that.

Ms. AUTOR. I don't think we know yet at what point in the supply chain the overly sulfated chondroitin sulfate would have been introduced. But we found it at various points in the supply chain. So if you are asking if it's an after-market addition, I think that is unlikely.

Mr. BURGESS. You think that is unlikely?

Ms. AUTOR. Yes.

Mr. BURGESS. So it was adulterated at the site of manufacture or multiple locations simultaneously?

Ms. AUTOR. I don't think we know yet. And it may not be one place or one point in the supply chain. But I think we know enough to think it is not always at the end of the supply chain.

Mr. BURGESS. Is there anything about the molecule for hypersulfated chondroitin sulfate that would allow you to trace it? Or is it pretty much ambiguous once it gets out there into the universe, you can't tell where it was manufactured or where it came from?

Dr. WOODCOCK. That would be fairly sophisticated, say, doing isotope analysis or something like that. We are working with our international counterparts. We had a meeting of international regulators several weeks ago.

And that's how we found this web from China, where it was originating. It didn't just come out of this plant, it came from many plants. The heparin sources around the world were contaminated. So that gives us a better picture, and we're continuing to collaborate with them.

But I think it will be hard to trace chemically.

Mr. BURGESS. OK.

I will yield back, Mr. Chairman.

Mr. STUPAK. If it came from many plants, as you just said, then have you inspected those plants it came from?

Dr. WOODCOCK. We haven't inspected them all. They didn't all ship into the United States.

Mr. STUPAK. I realize that. But there's nothing that prevents a drug from going from here to Germany—I mean, from China to Germany and then over from Germany to the U.S. if they originate out of China, is there?

Dr. WOODCOCK. Well, you can only import into the United States if you are approved for import in the United States. Many of these products——

Mr. STUPAK. Right. The only one that's not right now is Baxter International from that one location. That's the problem a lot of us are having.

Dr. WOODCOCK. Oh, I see. Well, many of them don't have approved NDAs or ANDAs. They aren't approved for marketing in the United States, and they are not shipping into the United States.

Mr. STUPAK. So you think.

Dr. WOODCOCK. As best we can tell. As I said, we need better IT systems and better systems at the border.

Mr. STUPAK. Let me ask you this. Let me ask you this. Exhibit 32 is the—you don't have to look at it. It's the Chinese patent for oversulfated chondroitin sulfate. And in 33, there's a U.S. patent.

And some of these go back to—well, the one actually goes back to 1967, 1978, 1980, 1989, 1989. The Chinese one is published in 2006.

Do you have any knowledge that oversulfated chondroitin sulfate has ever been used in the past as a blood thinner or an anticoagulant where it was polled or actually marketed oversulfated chondroitin sulfate?

I mean, it's interesting you have two patents, one in China and one here in the United States. And I would think that someone must have tried this in the past.

Dr. WOODCOCK. Right. There is also in here about anti-inflammatory and pain-killing activity. There is a product that had been marketed in Europe that was very similar.

Mr. STUPAK. Similar.

Dr. WOODCOCK. We don't have chemical comparison directly in the laboratory. But that was used in humans in Europe.

So these types of products, which are oversulfated gags, have been used, and there's certainly a lot of knowledge in the scientific literature that they have anticoagulant properties. So it's no secret that they have these activities.

Mr. STUPAK. Well, I just noticed, I thought the patent on the U.S. one actually mentioned heparin. That's why I—on page 2 of it, it sort of mentioned heparin. That's why I wanted to know if it had been used before, oversulfated chondroitin sulfate in heparin, to mimic as an anticoagulant. Probably, after you look at these patents, probably no big surprise that it happened this way.

Dr. WOODCOCK. I see. Well, it's certainly not approved in the United States. If it had been used somewhere in the world, it would be investigational use.

Mr. STUPAK. Thank you.

Seeing no further questions of this panel, I will excuse this panel and thank you for your time and testimony.

I will now invite our third panel of witnesses to come forward.

On our third panel we have Robert L. Parkinson, Jr., who is chairman, CEO, and president of Baxter International, Inc.; Mr. David Strunce, who is the chief executive officer of Scientific Protein Laboratories, LLC. Mr. Strunce is accompanied by Dr. Yan Wang, who is Scientific Protein Laboratories' vice president for business development and research.

Gentlemen, it's the policy of this subcommittee to take all testimony under oath.

Please be advised witnesses have the right, under the rules of the House, to be advised by counsel during their testimony. Do any of you wish to be represented by counsel today?

Mr. Parkinson, were you going to say something?

Mr. PARKINSON. Yes.

Mr. STUPAK. Do you wish to be represented by counsel? Would you turn on your mic and identify your counsel, just so we have it for the record? And they can advise you, but they can't testify.

Mr. PARKINSON. Yes. Mr. Ted Hester with King & Spalding.

Mr. STUPAK. OK, Mr. Hester.

Mr. Strunce—am I saying that right, Mr. Strunce?

Mr. STRUNCE. It's Strunce.

Mr. STUPAK. Do you wish to be represented by counsel?

Mr. STRUNCE. Yes, sir.

Mr. STUPAK. And would you identify that counsel for the record, please?

Mr. STRUNCE. Mr. Dan Kracov of Arnold & Porter.

Mr. STUPAK. OK.

Is it Mr. Wang?

Dr. WANG. Pronounced like W-O-N-G.

Mr. STUPAK. OK. Do you wish to be represented by counsel?

Dr. WANG. Yes.

Mr. STUPAK. Would you identify the counsel for the record?

Dr. WANG. Mr. Kracov.

Mr. STUPAK. OK, very good.

Again, counsel can advise you but cannot testify.

Therefore, I am going to ask you all to rise and raise your right hand and take the oath, please.

[Witnesses sworn.]

Let the record reflect the witnesses replied in the affirmative.

You are now under oath.

We will begin with a 5-minute opening statement from our third panel. I will start with Mr. Parkinson, if you would, please, sir. And if you have a longer statement, we will include it in the record.

If you would pull that forward, press that button there so your mic is on, and we will be ready to go.

STATEMENT OF ROBERT L. PARKINSON, JR., CHAIRMAN, CEO, AND PRESIDENT, BAXTER INTERNATIONAL, INC., DEERFIELD, ILLINOIS

Mr. PARKINSON. Good afternoon, Mr. Chairman and members of the Committee. My name is Bob Parkinson, and I am the chairman, chief executive officer and president of Baxter International. I'm very grateful for the opportunity to speak with you on the crucial topic of medical product safety.

Before I begin my formal opening comments, I would like to say a word to the families who took the time to be here today and make the effort to be here today. Like everyone in the room, I am tremendously moved by your testimony. I am terribly sorry for your loss. And I know that these are very painful circumstances, and you have my deepest sympathy.

Baxter has built its reputation over 75 years by consistently producing quality products for critically ill patients and patients with life-threatening diseases. We're alarmed that one of our products was used in what appears to have been a deliberate scheme to adulterate a life-saving medication, and that people have suffered as a result. We deeply regret that this has happened, and I feel a strong sense of personal responsibility for these circumstances. I feel this responsibility because of who we are and what we do as a company.

Each day, over 6 million infusions of Baxter's products are administered to patients around the world with life-threatening diseases and conditions. We're not a traditional pharmaceutical company. We don't make pills or tablets. We don't do direct-to-consumer advertising, and we don't make lifestyle drugs. We develop and manufacture products that are injected, infused, or inhaled by patients who need them to stay alive.

Because our products are used in critical-care environments, they have to be safe and effective every time. And this time they were not. No matter what the reason, this is my responsibility because Baxter's name was on the product. And my heart goes out to every patient and family member who may have been harmed by Baxter's heparin.

Members of the Committee, we all share the same objective: to ensure patient safety. And this presents an increasing challenge since, as the events of recent weeks demonstrate, we live in a world in which every day new risks are emerging.

I would refer the Committee to our written submission, which discusses the development of this situation, including what we at Baxter might have done differently, what we're doing going forward, and what we advocate for the industry and the global regulatory community.

What the developments of the last several weeks have taught us is that this is both a global and industry-wide crisis and, therefore, one that calls for global and industry-wide responses. Baxter played a leading role in finding and understanding this problem and in developing the test methods to detect it. And I commit to you that we will play a leading role in working with this committee, with regulators not only here but abroad, and with industry organizations to address this and other emerging risks for the long term.

Since coming to Baxter 4 years ago, I've been inspired by this special sense of purpose with which Baxter employees come to work every day. Because of our company's mission to sustain and save lives, anything that threatens that purpose cannot be tolerated. We welcome the opportunity to be part of this important discussion.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Parkinson follows:]

Testimony of Robert L. Parkinson
Chief Executive Officer, Baxter International
Before Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
April 29, 2008

Introduction

Good Morning Mr. Chairman and Members of the Committee. My name is Bob Parkinson, and I am Chairman, Chief Executive Officer and President of Baxter International (Baxter). I appreciate the opportunity to be here today to provide testimony and to respond to the Committee's questions on the crucial topic of medical product safety and the recent recall of heparin products that Baxter and many other companies have implemented.

Our mission at Baxter is to provide life saving and life sustaining medical therapies to patients across the world. We are not a traditional pharmaceutical company. Every one of the products we develop and manufacture is injected, infused or inhaled by patients who need them to stay alive. This is true across our three divisions: our Renal division provides dialysis therapies for patients with end-stage renal disease; our Bioscience division provides biologic therapies for patients with serious blood disorders like hemophilia or primary immune deficiency; and our Medication Delivery division provides a wide range of hospital products for use in acute and critical care settings. If you or a loved one has kidney failure; if your child was born without a functional immune system or with blood that doesn't clot; if you have the misfortune to find yourself in an intensive care unit, an emergency room or an operating room, Baxter products are the difference between life and death. In my four years at Baxter, I have been inspired by the extent to which this is a source of pride for Baxter employees, and it is the source of the profound commitment and responsibility we feel for each of our patients.

Baxter has been in business for over 75 years. More than any other company in the world, our products are involved in critical care settings. Because of this, we are greatly concerned that our heparin product appears to be the target of a deliberate adulteration scheme. Patient safety is our number one priority, and we deeply regret any harm this contamination in Baxter's heparin may have had on patients or impact on the clinicians who treat them.

Through Baxter collaboration with FDA, oversulfated chondroitin sulfate ("OSCS") was identified as a contaminant in certain lots of our injectable vial heparin product. Baxter scientists did not stop there, and in laboratory animal tests have observed a causal relationship between OSCS and hypotensive effects, the results of which were recently confirmed in an article published in The New England Journal of Medicine. Given the knowledge that we have developed over a short period of time, we have made a significant contribution to helping regulatory bodies and manufacturing companies around the world protect the world's heparin supply from this insidious contaminant.

Baxter's Manufacturing of Heparin

Baxter, and its predecessor company ESI Lederle (Wyeth), has been manufacturing heparin in a vial form for over 30 years. Baxter purchases heparin active pharmaceutical ingredient ("API") from Scientific Protein Laboratories ("SPL"), a company located in Waunakee, Wisconsin. Heparin API is derived from the mucosal lining of pig intestines. SPL initially sourced the crude material for its API from the United States. In the mid-1990s, SPL embarked on a program to find other raw material suppliers to assure a consistent quality supply of heparin. Because of supply constraints around the world, SPL, like virtually all heparin API manufacturers, began sourcing this product from raw material suppliers in China, the source of over half of the world's pig supply. ESI and Baxter consistently manufactured heparin made from SPL's API, sourced from Chine crude, since 1996.

In order to be closer to its Chinese supply chain and to increase its manufacturing capabilities, SPL built a heparin API manufacturing facility in Changzhou, China (SPL-CZ) in 2000. In December 2002, Wyeth Global Compliance performed a qualifying audit of this facility. The facility had run three consecutive validation lots before this inspection. Baxter acquired ESI shortly after this audit. Baxter undertook the process of having SPL-CZ qualified by the FDA as a supplier of heparin API. Baxter submitted a Prior Approval Supplement (PAS) to the FDA on February 6, 2004. The PAS requested that the FDA approve "Changzhou-SPL Co., Ltd. as an alternate supplier" for heparin.

On June 8, 2004 FDA sent a letter to Baxter approving SPL-CZ as an alternate supplier for heparin. Once we received that approval, the manufacture of the API from this facility was approved by the FDA. That approval was not subject to or conditioned on an FDA inspection.

Speaking for Baxter, however: we don't rely on FDA inspections to ensure the quality of our product – that's our job, independent of the FDA's role.

To fulfill this obligation, Baxter relied on Wyeth's December 2002 qualifying audit. In hindsight, we should have conducted our own qualification audit as well, before beginning to receive product in 2004. It bears noting, however, that plant audits were not the only thing we relied on to ensure the quality of our product – we also consistently monitored the quality of both the incoming product we received from SPL and the finished heparin product that we released. Although sample testing is regulatorily acceptable, we tested each and every lot. Our testing exceeded the standards of the U.S. Pharmacopoeia ("USP"), the official public authority that sets standards for all healthcare products sold in the United States. The USP standards for heparin have been successfully used for decades. Unfortunately, we now know that these standards were insufficient to detect this new heparin-like contaminant because OSCS could not be detected with established and validated test procedures. Going forward, Baxter is committed to working with USP and FDA in re-evaluating standard heparin test procedures.

Baxter's Quality team performed a cGMP audit of the SPL-CZ facility in September 2007. The audit consisted of an in-depth review of CZ SPL's quality systems and capabilities including, but not limited to, its supply chain quality systems, such as the documentation and procedures associated with incoming materials and sampling. Baxter was assured that SPL's QA department audits the workshops it uses on an annual basis. SPL also provided assurances that these workshops collect veterinary data for all porcine sources to assure the stock is disease-free prior to collection.

Baxter's Recall of Heparin

Heparin vials are used in a variety of critical care settings, including cardiac and dialysis procedures. Allergic-type reactions are indicated in the label for heparin, and every year Baxter receives approximately 30 reports of adverse events associated with its heparin vial products. At the very end of December 2007 and the beginning of January 2008, we noticed an increase in the rate of reported allergic-type reactions associated with its 1,000 unit/mL multi-dose heparin product, and we launched an investigation. The initial reports came from dialysis centers, so Baxter physicians and quality professionals traveled to reporting dialysis centers. We also began an investigation of our own manufacturing and quality procedures and records for heparin. We also ceased all production and distribution of this heparin product.

After additional adverse event reports came in from other facilities, Baxter (in consultation with FDA) recalled nine lots of its 1,000 unit/mL heparin product that were associated with these adverse events on January 17, 2008. After this recall was announced, we saw a slight increase in reactions in other lots and sizes of heparin. We contacted FDA about expanding the recall. Based on FDA's market data, both we and FDA were concerned about a shortage of heparin. On February 8, 2008 Baxter and FDA concluded that it was better for the public health to allow Baxter's product to remain in distribution so it could be used with caution in situations where the use of heparin was medically necessary and alternate sources of heparin were not available. Baxter sent an Important Safety Information Bulletin to thousands of health care providers on February 11, 2008, apprising them of this situation. When we read that another supplier of heparin said it had the ability to source the U.S. heparin market, we asked FDA for confirmation and, upon receiving it, we expanded our heparin recall on February 28, 2008.

During this recall, Baxter informed health care professionals, customers, renal home care patients, wholesalers, distributors and known customers of wholesalers and distributors by mailing thousands of letters via overnight mail about the recall. Baxter also called thousands of renal home patients directly to discuss the recall. Frequent press releases were issued, a press conference was held, a hotline was staffed and information about the recall was regularly posted on Baxter's website.

Baxter's Investigation of Root Cause

Baxter has been thoroughly investigating the potential cause of the increase in adverse event reports. After multiple variables were ruled out in the manufacturing process and the supply chain, we began to focus on possible issues in the heparin API. Baxter has devoted more than 30 scientists to this investigation and has employed distinguished outside scientists as consultants. Most of our scientists are based at the company's laboratories in Illinois, although we also took advantage of the expertise of Baxter scientists in Europe. We worked openly and diligently in collaboration with FDA on our analytical results. A wide variety of laboratory methodologies and hundreds of different tests were employed in these investigations, including state-of-the-art analytical instrumentation tests such as nuclear magnetic resonance spectroscopy (NMR) and capillary electrophoresis (CE). Using these tests, it was determined that extra signals and a peak were detected in the heparin associated with the recall (test) compared to heparin that was not associated with the recall (control). The contaminant from the test lots was identified as OSCS.

NMR and CE tests have confirmed that the contaminant found in the API was also found in the crude heparin supply. According to early reports, similar peaks were found in Australia in AstraZeneca's heparin as well as in Germany in RotexMedica's heparin. Neither of these companies received their supply of heparin API from SPL. Since then, the FDA has reported that multiple companies in 11 countries have found this contaminant. Based on the appearance of OSCS in the crude heparin material coming into SPL, and on the fact that other companies with other suppliers have also had OSCS contamination, it is clear that OSCS was added farther up the supply chain, before the crude material reached SPL. Baxter is still trying to understand where exactly the contaminant was introduced.

The introduction of OSCS was difficult to detect because of how closely this contaminant mimicked heparin. Heparin is the most highly charged molecule found naturally in living systems. As such, it is an extremely polar molecule and requires an extremely polar solvent, like water, to stay in solution. In normal heparin production, the heparin is the most polar molecule among the normal constituents of crude heparin (including dermatan sulfate and chondroitin sulfate). OSCS contains more sulfate groups than does heparin, making it more polar than heparin, and making it the first material to lose solubility when ethanol is added to the aqueous solution of impure heparin. Thus, the OSCS is precipitated along with the heparin. In a process designed to collect the most polar material from solution, the OSCS is collected with the heparin.

Over the last few weeks, our investigation has focused on biologic tests aimed at determining whether there is any relationship between OSCS and the increased adverse events that were associated with this recall. The most common adverse event reported was hypotension. Baxter scientists were able to establish that OSCS can cause hypotensive reactions – that is, consistent, prolonged declines in blood pressure – in laboratory animals. They found the same results from exposure to heparin contaminated with OSCS. The hypotensive response was dose-dependent; increased amounts of the OSCS or the contaminated heparin led to greater decreases in blood pressure. Baxter scientists are still searching to understand the cause of a decrease in blood pressure in humans. This result is consistent with the New England Journal of Medicine study in which scientists found a scientific rationale for a potential biologic link between the presence of OSCS and observed clinical adverse events. That article, a copy of which is attached, reached this conclusion: "Our results provide a scientific rationale for a potential biological link between the presence of OSCS in suspect lots of heparin and the observed clinical adverse events."

Recall of Heparin Around the World

OSCS, the apparent cause of the increase in heparin adverse events, is a very effective imposter that mimics heparin. Not only did this substance avoid detection through long-established USP testing, it avoided detection through the quality systems of several major pharmaceutical companies around the globe, and through the oversight of regulatory authorities in countries around the world, including Australia, Canada, China, Denmark, France, Germany, Italy, Japan, The Netherlands and New Zealand. Because of the swift identification of OSCS and advanced NMR and CE tests methods to detect it, FDA and regulatory authorities around the world have been able to respond proactively, averting a much broader crisis by detecting and screening out the contaminant in other manufacturers' heparin before it was more broadly distributed to patient populations. Baxter continues to cooperate with Ministries of Health around the world and share information we and they have learned about OSCS, including how to detect the presence of OSCS in heparin API and finished product.

Corrective Actions

The developments of the last several weeks have demonstrated that this is both a global and industry-wide crisis, with a root cause that was so novel and so insidious as to avoid the quality systems of a multitude of companies and the oversight of the world's most sophisticated drug regulatory agencies. This extraordinary problem calls for extraordinary corrective actions. It is important to harness the resources and thinking of the entire industry and the global regulatory community to address those new and emerging risks, both deliberate and not, that threaten the safety of life-saving drugs and biologics. In particular:

- Baxter is methodically re-examining our global supply chain practices in light of the heparin mimic that surfaced here, to assess whether unexpected vulnerabilities exist in the supply chain *beyond* our direct suppliers. This review is necessarily going above and beyond current regulatory requirements and industry standards, which proved inadequate to detect this problem. Although less than 1% of all Baxter products sold in the U.S. include components sourced from China, we are beginning our evaluation with a thorough review of our China-based suppliers and their sources. We have retained recognized experts in supply chain management strategy to assist us in this effort.

- Based on what this full-scale evaluation tells us, we will impose targeted prevention and detection methods on our suppliers to limit exposure to vulnerabilities that exist in their supply chains.
- We have convened a group of Baxter scientists whose mission will be to consider how would-be counterfeiters or saboteurs might threaten our supply chain, much the way that law enforcement or national security agencies have groups dedicated to thinking like potential enemies. By directing outstanding scientific minds at this kind of question, our aspiration is to imagine, address and prevent this kind of threat before it happens. Going forward, we will try to anticipate the unanticipated.
- We believe this type of supply chain threat evaluation is something the FDA and the global regulatory community ought to require more broadly of industry participants. Moreover, we would encourage these agencies to facilitate collaboration on and sharing of these efforts, since the positive changes that could result will be effective only if they are consistently applied and enforced across the industry. Just as the fruits of Baxter's and the FDA's efforts to identify and test for OSCS were immediately shared with the industry in *reaction* to a problem, the world's patients and the global drug and biologic supply would far better served if the fruits of these *proactive* analyses were a common asset for the public good.

Conclusion

Baxter's quality systems for heparin have come under intense scrutiny as a result of this recall. We believe our quality systems are robust, but no quality system is bullet proof. We certainly acknowledge that we should have conducted our own qualification audit of the facility, rather than relying on our predecessor's audit. Importantly, it is not clear that such an additional inspection would have detected or prevented the OCSC contaminant. Therefore, it would be wrong for us to ascribe this problem to a missed inspection and move forward based on improved inspection frequency. Indeed, such a reaction would miss the real points: that the complexity of the global drug supply chain creates new and emerging risks that call for new ways of thinking about, identifying and addressing vulnerabilities, and that resting on old standards – even ones that have worked for decades – is no longer enough. These are the most critical lessons of this entire crisis, and Baxter embraces them.

Baxter fully supports the allocation of increased resources for FDA. Baxter references the statements by Commissioner von Eschenbach (in testimony last week before this Subcommittee) that FDA lacks adequate resources to conduct effective overseas inspections and to keep a modern and effective database of foreign firms processing products for US patients. We support funding directed to enhancing FDA's ability to fulfill its mission of providing safe and effective products to the American people, and we welcome any opportunity to work with Congress and the Agency in support of this mission.

We appreciate the Committee's interest in medical product safety, and we fully support the Committee's goals. Baxter is eager to continue collaborating with this Committee and others to ensure the safety of heparin. This has been a learning experience for Baxter, and I hope it can be a learning experience for the entire global industry and the global regulatory community so we can all work together to ensure that these types of incidents never happen again. Thank you for giving me the opportunity to be part of this important discussion.

Testimony of Robert L. Parkinson
Chief Executive Officer, Baxter International
Before Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
April 29, 2008

SUMMARY OF MAJOR POINTS

- More than any other company in the world, Baxter's products are involved in critical care settings. Because of this, we are greatly concerned that our heparin product appears to be the target of a deliberate adulteration scheme. Patient safety is our number one priority, and we deeply regret the impact this contamination in Baxter's heparin has had on patients and the clinicians who treat them.
- The developments of the last several weeks have demonstrated that this is both a global and industry-wide crisis, with a root cause – oversulfated chondroitin sulfate ("OSCS") -- that was so novel and so insidious as to avoid the quality systems of a multitude of companies and the oversight of the world's most sophisticated drug regulatory agencies.
- Because of the swift identification of OSCS, and the development of advanced NMR and CE tests methods to detect it, FDA and regulatory authorities around the world have been able to respond proactively, averting a much broader crisis by detecting and screening out the contaminant in other manufacturers' heparin before it was more broadly distributed to patient populations.
- The complexity of the global drug supply chain creates new and emerging risks that call for new ways of thinking about, identifying and addressing vulnerabilities. Resting on old standards – even ones that have worked for decades – is no longer enough. These are the most critical lessons of this entire crisis, and Baxter embraces them.
- We support funding directed to enhancing FDA's ability to fulfill its mission of providing safe and effective products to the American people, and we welcome any opportunity to work with Congress and the Agency in support of this mission.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Takashi Kei Kishimoto, Ph.D., Karthik Viswanathan, Ph.D., Tanmoy Ganguly, Ph.D., Subbiah Elankumaran, Ph.D., Sean Smith, B.S., Kevin Pelzer, Ph.D., Jonathan C. Lansing, Ph.D., Nammalwar Sriranganathan, Ph.D., Ganlin Zhao, M.D., Zoya Galcheva-Gargova, Ph.D., Ali Al-Hakim, Ph.D., Gregory Scott Bailey, B.S., Blair Fraser, Ph.D., Sucharita Roy, Ph.D., Thomas Rogers-Cotrone, M.S., Lucinda Buhse, Ph.D., Mark Whary, Ph.D., James Fox, Ph.D., Moheb Nasr, Ph.D., Gerald J. Dal Pan, M.D., Zachary Shriver, Ph.D., Robert S. Langer, Sc.D., Ganesh Venkataraman, Ph.D., K. Frank Austen, M.D., Janet Woodcock, M.D., and Ram Sasisekharan, Ph.D.

ABSTRACT

BACKGROUND

There is an urgent need to determine whether oversulfated chondroitin sulfate (OSCS), a compound contaminating heparin supplies worldwide, is the cause of the severe anaphylactoid reactions that have occurred after intravenous heparin administration in the United States and Germany.

METHODS

Heparin procured from the Food and Drug Administration, consisting of suspect lots of heparin associated with the clinical events as well as control lots of heparin, were screened in a blinded fashion both for the presence of OSCS and for any biologic activity that could potentially link the contaminant to the observed clinical adverse events. In vitro assays for the activation of the contact system and the complement cascade were performed. In addition, the ability of OSCS to recapitulate key clinical manifestations in vivo was tested in swine.

RESULTS

The OSCS found in contaminated lots of unfractionated heparin, as well as a synthetically generated OSCS reference standard, directly activated the kinin–kallikrein pathway in human plasma, which can lead to the generation of bradykinin, a potent vasoactive mediator. In addition, OSCS induced generation of C3a and C5a, potent anaphylatoxins derived from complement proteins. Activation of these two pathways was unexpectedly linked and dependent on fluid-phase activation of factor XII. Screening of plasma samples from various species indicated that swine and humans are sensitive to the effects of OSCS in a similar manner. OSCS-containing heparin and synthetically derived OSCS induced hypotension associated with kallikrein activation when administered by intravenous infusion in swine.

CONCLUSIONS

Our results provide a scientific rationale for a potential biologic link between the presence of OSCS in suspect lots of heparin and the observed clinical adverse events. An assay to assess the amidolytic activity of kallikrein can supplement analytic tests to protect the heparin supply chain by screening for OSCS and other highly sulfated polysaccharide contaminants of heparin that can activate the contact system.

From Momenta Pharmaceuticals (T.K.K., T.G., S.S., J.C.L., G.Z., Z.G.-G., G.S.B., S.R., Z.S., G.V.) and the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Koch Institute for Integrative Cancer Research (K.V., Z.S., R.S.L., G.V., R.S.) — both in Cambridge, MA; Virginia–Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg (S.E., K.P., N.S., T.R.-C.); the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD (A.A.-H., B.F., L.B., M.N., G.J.D.P., J.W.); the Massachusetts Institute of Technology, Cambridge, MA (M.W., J.F.), and Brigham and Women's Hospital and Harvard Medical School, Boston (K.F.A.). Address reprint requests to Dr. Sasisekharan at the Department of Biological Engineering, Harvard–MIT Division of Health Sciences and Technology, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Ave., 16-561, Cambridge, MA 02139, or at rams@mit.edu.

This article (10.1056/NEJMoa0803200) was published at www.nejm.org on April 23, 2008.

N Engl J Med 2008;358.

Copyright © 2008 Massachusetts Medical Society.

IN JANUARY 2008, HEALTH AUTHORITIES IN the United States began receiving reports of clusters of acute hypersensitivity reactions in patients undergoing dialysis that had been occurring since November 2007. Symptoms included hypotension, facial swelling, tachycardia, urticaria, and nausea. Although initial investigations focused on dialysis equipment, an investigation by the Centers for Disease Control and Prevention identified the receipt of heparin sodium for injection (1000 U per milliliter, in 10-ml and 30-ml multidose vials), manufactured by Baxter Healthcare, as a common feature of the cases.[1] This finding led Baxter Healthcare to recall, on January 17, 2008, nine lots of heparin sodium for injection. As of April 13, 2008, there were 81 reports of death that involved at least one sign or symptom of an allergic reaction or hypotension in patients receiving heparin since January 1, 2007. However, the fact that allergic symptoms or hypotension were reported does not mean that these were the cause of death in all cases.

After this initial recall, there were continuing reports of allergic-type reactions, including some deaths, after injection of bolus heparin not only in patients undergoing dialysis but also in patients in other clinical settings, such as those undergoing cardiac procedures. On February 28, 2008, Baxter Healthcare recalled all remaining lots and doses of its multidose and single-dose vials of heparin sodium for injection and HEP-LOCK heparin flush products. Since that recall, monitoring by the Food and Drug Administration (FDA) has indicated that, in March 2008, the number of deaths reported in association with heparin usage had returned to baseline levels.[2]

However, on March 6, a heparin recall was announced in Germany because of a cluster of reactions in patients undergoing dialysis that were linked to a different manufacturer's heparin. On the same day, the FDA posted descriptions of analytic methods on its Web site and recommended that all manufacturers and regulatory authorities screen for a contaminant in heparin.[3] This screening revealed widespread contamination of the heparin supply in at least 12 countries.

The contaminant was recently identified as an unusual oversulfated form of chondroitin sulfate (OSCS) representing up to approximately 30% wt/wt in suspect lots of heparin; no other contaminants were observed.[4] In addition, dermatan sulfate, a known impurity of heparin, was found in selected samples. Both heparin and chondroitin sulfate are members of the glycosaminoglycan family of complex polysaccharides; heparin contains a disaccharide repeat unit of glucuronic–iduronic acid linked to glucosamine, and chondroitin sulfate contains a disaccharide repeat unit of glucuronic acid linked to galactosamine. Analysis of the contaminant unexpectedly revealed an unusual type of sulfation not found in any natural sources of chondroitin sulfate and indicated that OSCS, containing four sulfates per disaccharide unit, is structurally similar to heparin (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

However, the biologic link between the presence of the OSCS in heparin and the adverse clinical events remained to be established. Highly charged polyanionic polymers are known to modulate various enzymatic cascades in plasma, affecting coagulation, fibrinolysis, inflammation, and vasculature function.[5,6] Bradykinin, a potent vasoactive peptide mediator, is generated through the activation of the contact system of coagulation, which is initiated upon contact of factor XII with a negatively charged surface in the presence of prekallikrein and high-molecular-weight kininogen. Highly sulfated polysaccharides have been shown to serve as a negatively charged surface that can initiate fluid-phase activation of the contact system.[5,7] However, initial attempts to recapitulate the adverse responses in experimental models were unsuccessful.[8] Without a definitive link between the contaminant and the clinical reactions, concerns remain that the screening tests currently in place may not be adequate to prevent further cases. We therefore set out to identify a biologic basis for a link between OSCS and allergic-type reactions.

CASE REPORT

A representative case involved a 63-year-old woman with a complex medical history, including end-stage renal disease treated with the use of hemodialysis for 7 years, who received heparin intravenously during hemodialysis (5000-U loading dose and 500 U per hour during the procedure) three times weekly. In mid-January 2008, the development of "low blood pressure" was reported, along with nausea and dyspnea, during dialysis. She was treated with normal saline and

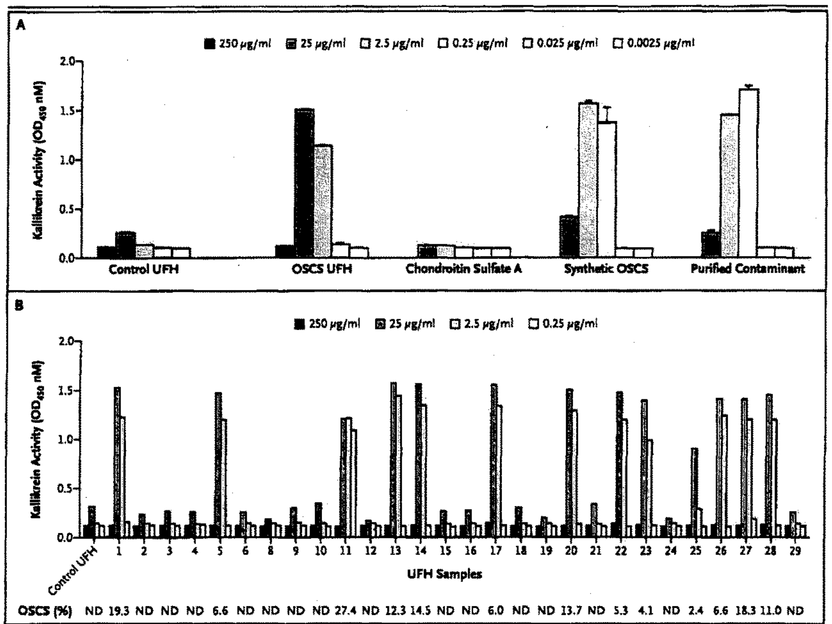


Figure 1. Effect of OSCS on Kallikrein Activity.

Pooled human plasma samples were treated with control unfractionated heparin (UFH) or OSCS-contaminated heparin (0.025 to 250 μg per milliliter) or with chondroitin sulfate A, synthetic OSCS, or purified OSCS contaminant (0.0025 to 25 μg per milliliter). Amidolytic activity was assessed by the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline); the effect on kallikrein amidolytic activity is shown (Panel A). The presence of OSCS in heparin was associated with the induction of kallikrein activity. Twenty-nine samples of heparin, representing both suspect heparin lots and control lots, were analyzed in a blinded fashion for both the presence of OSCS and the ability to activate kallikrein (Panel B). The presence of OSCS was detected and quantified by one-dimensional nuclear magnetic resonance spectroscopy (see Figure 2 in the Supplementary Appendix). The percentage of each sample that was OSCS is shown below the plot. Kallikrein amidolytic activity was assessed at various concentrations of heparin; Sample 7 was not analyzed for kallikrein activity owing to the limited quantity available. ND denotes not detectable, and OD optical density.

oxygen (2 liters per minute), and the rates of ultrafiltration and blood flow were slowed. She recovered after 30 minutes, and dialysis was continued. Two days later, she again received intravenous heparin (5000-U loading dose and 500 U per hour) from the same lots of heparin from the same manufacturer (Baxter Healthcare). Immediately after dialysis was initiated, the patient had an anaphylactoid reaction, with a sudden drop in blood pressure (to 65/34 mm Hg), dyspnea, nausea, vomiting, and constitutional symptoms. She was treated with a bolus of normal saline and oxygen (2 liters per minute). Hemodialysis was continued for another hour. The patient continued to feel ill, was admitted to the hospital, and was discharged 2 days later, after recovery. Further dialysis was performed with the use of heparin from another manufacturer.

METHODS

TEST SAMPLES

Twenty-nine clinical lots of heparin, including 13 associated with clinical adverse events, were procured from the FDA and coded as unknown samples 1 through 29. A laboratory lot of heparin was included as a control. For all analytic and biologic tests, samples were dosed on a weight basis; specific activity of heparin is typically approximately 180 U per milligram. OSCS was purified to homogeneity from a lot of heparin that was known to be contaminated, as previously described.[4] Briefly, OSCS-contaminated heparin was subjected to anion-exchange chromatography followed by alcohol precipitation to isolate the contaminant.[4] The identity of the contaminant was confirmed by means of multiple orthogonal techniques, including multidimensional nuclear magnetic resonance (NMR), enzymatic digestion followed by high-performance liquid chromatography, and liquid chromatography–mass spectrometry.[4] After identification of the contaminant as OSCS, a synthetic standard was generated through chemical sulfonation of chondroitin sulfate A and was exhaustively characterized to ensure authenticity, as previously described.[4] The synthetic OSCS was used in spiking experiments to qualify the analytic procedures (especially one-dimensional proton NMR, described below) to determine limits of detection and to establish accurate quantification.[4] The limit of detection for this assay was determined to be 0.3% on a weight basis for both dermatan sulfate and OSCS.

ANALYTIC METHODS

To ensure accurate identification and quantification of any contaminants and impurities, the 29 coded test samples were subjected to orthogonal analytic techniques. Proton NMR, anion-exchange chromatography, and capillary electrophoresis were used to screen the samples for the presence of OSCS, dermatan sulfate, and other nonheparin components. The levels of OSCS and dermatan sulfate were quantified with the use of a 600-MHz NMR instrument to ensure peak resolution. The details of quantification, as well as a representative spectrum, are given in Figure 1 and Table 1 in the Supplementary Appendix. For samples with unusual patterns, the identity of contaminants or impurities, including OSCS, was confirmed by means of detailed characterization, including the use of multidimensional NMR.[4]

AMIDOLYTIC ACTIVITY OF KALLIKREIN

Pooled human plasma or factor XII–depleted plasma (American Diagnostica) was treated with various concentrations of coded test samples of heparin, chondroitin sulfate A, or synthetic OSCS for 5 minutes at 37°C. The amidolytic activity of kallikrein (with a small contribution of factor XII)[9] was assessed by adding the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline [pNA]) for 30 minutes at 37°C, followed by spectrophotometric measurement of the absorbance at 450 nM.

GENERATION OF C3a AND C5a

Pooled human EDTA plasma or factor XII–depleted plasma (American Diagnostica) was treated with various concentrations of OSCS-contaminated heparin, control heparin, chondroitin sulfate A, or synthetic OSCS for 30 minutes at 37°C. C3a and C5a activation products of the complement cascade were assayed by means of a sandwich enzyme-linked immunosorbent assay (ELISA), as specified in the manufacturer's instructions (Becton Dickinson and Integrated Biotech Laboratories for C3a and C5a, respectively).

IN VIVO STUDIES

The swine were handled and treated in compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and the federal Animal Welfare Act. The experimental procedures were performed according to the Institutional Animal Care and Use Committee–approved protocol of the Virginia Polytechnic Institute and State University, Blacksburg, Virginia. Domestic Yorkshire crossbred swine were of either sex (Virginia Polytechnic Institute and State University) and ranged in weight from 10 to 25 kg. They were initially anesthetized with an intravenous injection of 6 mg of tiletamine hydrochloride per kilogram of body weight and 2.2 mg of xylazine per kilogram, and then a single-lumen silicone catheter was implanted in the left jugular vein of each animal. Adequate anesthesia was maintained throughout the procedure with the administration of supplemental tiletamine. After a 5-minute stabilization period, each pig received an intravenous bolus infusion of 5 mg of the test substance per kilogram (three to six pigs per test substance). All the pigs were continuously monitored for vital signs with the use of an oscillometric blood pressure monitor (Cardell 9401/9403, CAS Medical Systems) for systolic, diastolic, and mean arterial blood pressures, pulse oximetry for pulse and respiratory rates, and a rectal probe for body temperature. At the end of the 60-minute observation period, the animals were euthanized with the use of an intravenous infusion of Fatal Plus (Vortech Pharmaceuticals) at a dose of

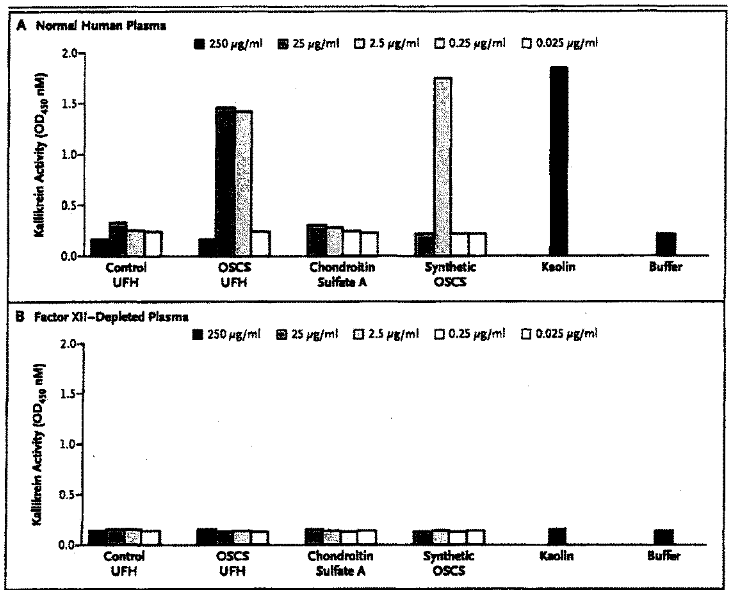


Figure 2. OSCS-Induced Activation of Kallikrein in Normal or Factor XII–Depleted Plasma.

Control unfractionated heparin (UFH), OSCS-contaminated UFH, chondroitin sulfate A, and synthetic OSCS were incubated with normal plasma (Panel A) or with factor XII–depleted plasma (Panel B); OSCS-induced activation of kallikrein is dependent on factor XII, as indicated. Kaolin-containing buffer was evaluated as a positive control activator of the contact system. Buffer alone was included as a negative control. Amidolytic activity was assessed by the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline). OD denotes optical density.

0.22 ml per kilogram. Blood samples were collected at baseline and at 5, 10, 20, 40, and 60 minutes and were kept in 5 mM EDTA. Plasma was isolated after centrifugation at 4°C and flash-frozen on dry ice. Frozen samples were thawed at 4°C and assayed for amidolytic activity of kallikrein with the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-pNA), as described above.

RESULTS

Given the association of activation of the contact system with negatively charged polysaccharides, we sought to elucidate whether an in vitro biologic response could be correlated with the identity or levels of contaminant within heparin lots. To this end, we examined the ability of a sample of OSCS-contaminated heparin, containing 19.3% wt/wt OSCS (Table 1 in the Supplementary Appendix), to activate kallikrein amidolytic activity in human plasma (Fig. 1A). The contaminated heparin showed a bell-shaped dose response, which is typical of glycosaminoglycan-mediated responses.[5,10] At 2.5 and 25 μg per milliliter, robust activation of kallikrein was found with the contaminated heparin sample but not with a control sample of uncontaminated heparin. These concentrations are in the range of a clinically efficacious concentration of heparin of approximately 1 to 5 μg per milliliter, based on a specific activity of about 180 U per milligram. High concentrations of the OSCS-contaminated heparin (250 μg per milliliter) induced little or no amidolytic activity of kallikrein, suggesting that at this concentration, heparin may inhibit or cause depletion of factor XII, as previously described.[7,11,12] This high concentration of heparin also prevented

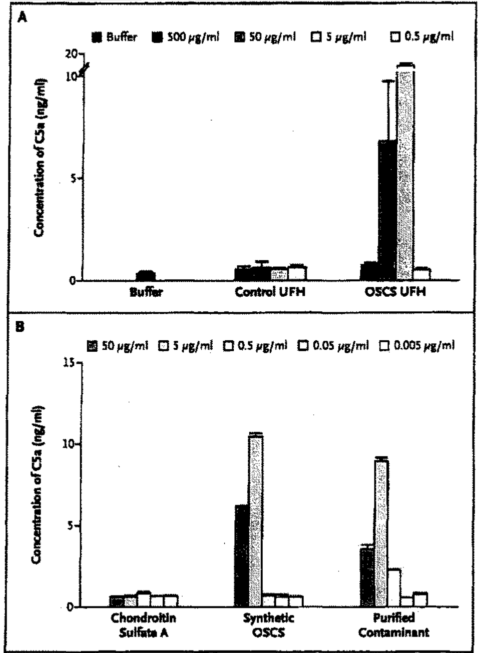


Figure 3. OSCS and the Generation of Complement-Derived C5a Anaphylatoxin in Human Plasma.

OSCS-contaminated unfractionated heparin (UFH) and control UFH (0.5 to 500 μg per milliliter) (Panel A) or chondroitin sulfate A, synthetic OSCS, and purified OSCS contaminant (0.005 to 50 μg per milliliter) (Panel B) were incubated with normal plasma anticoagulated with EDTA. The generation of C5a was assessed by ELISA.

activation of the contact system in response to kaolin, a potent activator (data not shown).

To further verify that the contaminant was responsible for the activation of the contact system, OSCS was purified to homogeneity by means of anion-exchange chromatography followed by alcohol precipitation. In addition, an OSCS standard was created through chemical sulfonation of chondroitin sulfate A, to form OSCS.[4] The purified contaminant and the OSCS standard were identical, as judged by several orthogonal analytic techniques, including two-dimensional NMR.[4] Both the purified contaminant and the synthetic OSCS showed robust activation of kallikrein activity at 0.25 μg and 2.5 μg per milliliter (Fig. 1A). The peak activity of the purified contaminant and the synthetic OSCS standard were observed at a level that was approximately an order of magnitude lower than that found for the contaminated heparin sample. This is consistent with the observation that the OSCS constituted approximately 20% of the contaminated sample. Chondroitin sulfate A showed no induction of amidolytic activity.

These results are in good agreement with the observations of Hojima et al.,[5] who demonstrated that oversulfated chondroitin, but not chondroitin A, B, or C, can activate the kinin pathway. Heparin also activated the contact system in an in vitro model system involving purified protein components[5,13] but did not in plasma,[13] suggesting that negative-regulatory factors present in plasma may prevent activation of the contact system by heparin. One such mechanism is the fact that heparin is known to enhance antithrombin III–mediated inhibition of factor XII. Our results indicate that OSCS, in contrast to heparin but similar to dextran sulfate,[13] can activate the contact system in plasma.

The 29 heparin samples procured from the FDA, consisting of both suspect heparin lots associated with clinical events as well as control heparin lots, were screened in a blinded fashion for both the presence of OSCS and the ability to activate the contact system (Fig. 1B). There was complete correspondence between the presence of detectable amounts of OSCS by one-dimensional proton NMR and the ability of a sample to induce robust amidolytic activity of kallikrein (Fig. 1B). The biologic activity was generally characterized as an all-or-none response, with all 13 samples containing detectable levels of OSCS having a positive response at 25 μg or 2.5 μg per milliliter. Sample 11, which contained the highest level of contaminant (27.4%), also showed activity at 0.25 μg per milliliter, whereas Sample 25, which contained the lowest level of contaminant (2.4%), showed only modest activity at 2.5 μg per milliliter. In contrast, there was no association between the level of inducible kallikrein activity and the level of dermatan sulfate (Fig. 2 in the Supplementary Appendix), an impurity found in many heparin preparations.

Direct activation of the contact system by the contaminated heparin and the synthetic OSCS standard was confirmed through the use of hu-

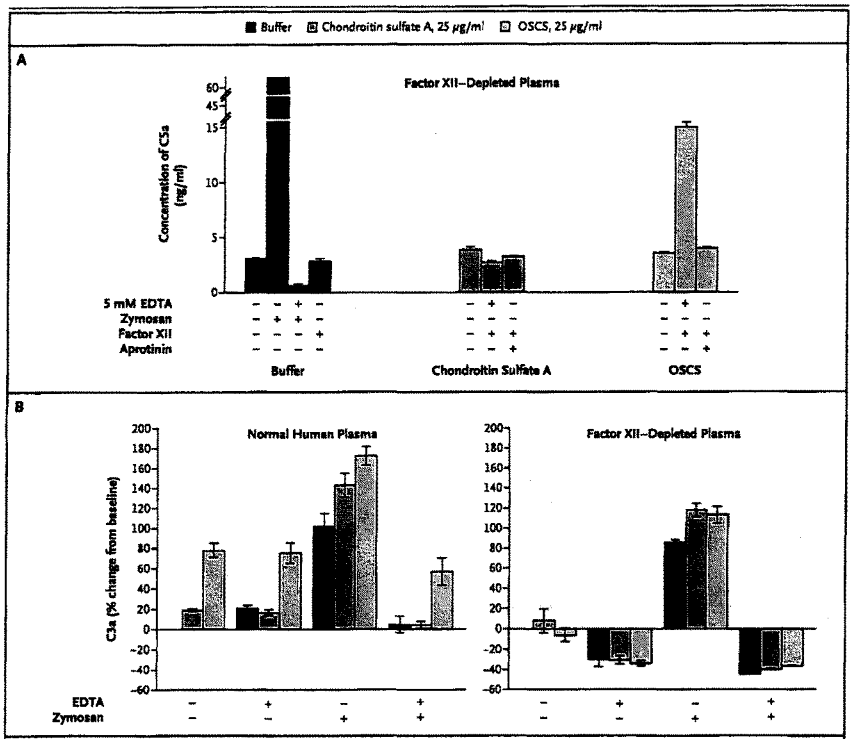


Figure 4. OSCS Induction of Complement-Derived C3a and C5a Anaphylatoxins and Its Relationship to the Contact System.
Factor XII–depleted plasma was incubated with chondroitin sulfate A, OSCS, or control buffer in the presence or absence of 5 mM EDTA, zymosan (1 mg per milliliter), or aprotinin (400 IU per milliliter) (Panel A). Specific samples were reconstituted with purified factor XII, as indicated. Normal human plasma or factor XII–depleted plasma was incubated with chondroitin sulfate A, OSCS, or control buffer in the presence or absence of 5 mM EDTA, zymosan (1 mg per milliliter), or both (Panel B). C3a and C5a generation was assessed by means of enzyme-linked immunosorbent assay (ELISA).

man plasma depleted of factor XII, the upstream activator of prekallikrein[14] (Fig. 2). The contaminated heparin, the synthetically derived OSCS, and the positive control (the kaolin-containing reagent) all failed to induce the amidolytic activity of kallikrein in factor XII–deficient plasma.

We next examined the ability of contaminated heparin to generate C3a and C5a, potent anaphylatoxins derived from complement proteins. Exposure of human plasma to the contaminated heparin, but not to control heparin, induced the production of C5a (Fig. 3). OSCS-induced C5a generation showed a bell-shaped dose response similar to that found for kallikrein activation. Peak C5a activity was observed at 50 μg and 5 μg per milliliter of heparin containing 19.3% OSCS. At 500 μg per milliliter, significant generation of C5a was not observed. Similar results were obtained with the purified OSCS isolated from contaminated heparin and the synthetic OSCS standard, but not with chondroitin sulfate A.

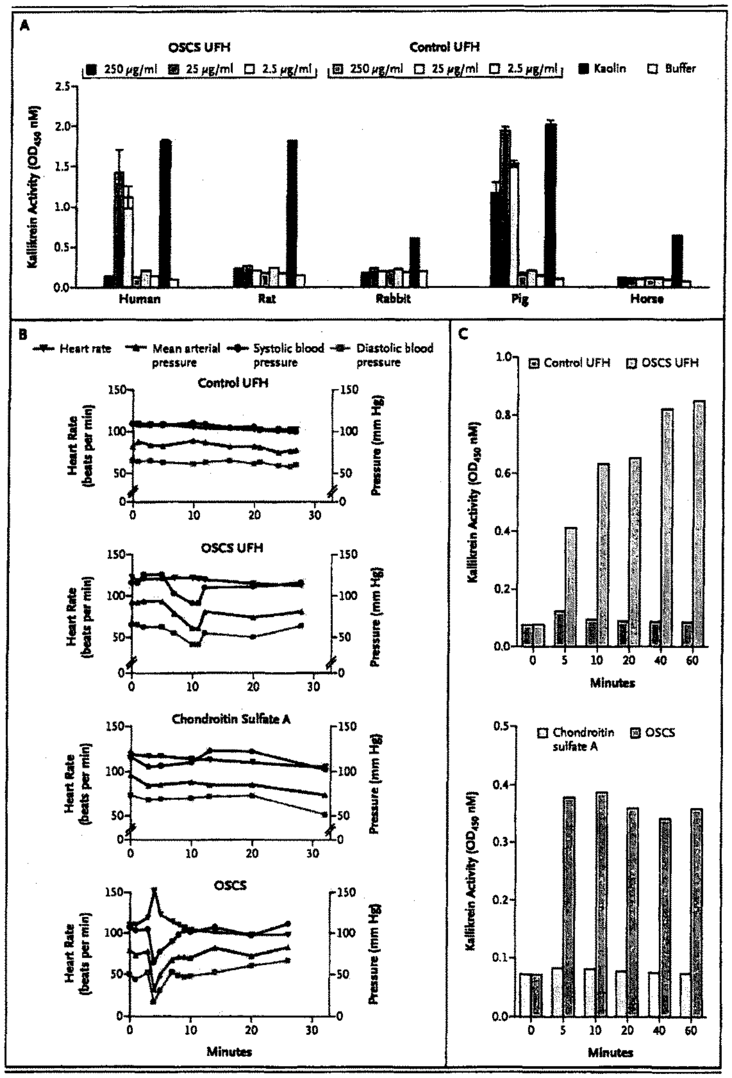
Surprisingly, the generation of C5a by OSCS-contaminated heparin was more robust in the presence of EDTA, a Ca^{2+}- and Mg^{2+}-chelating agent, than in the absence of EDTA. The classic and alternative pathways of complement activation are known to be dependent upon Ca^{2+} and Mg^{2+}, respectively. As expected, EDTA blocked C3a and C5a generation in response to zymosan, a potent activator of the alternative pathway (Fig. 4). These results suggested the possibility that OSCS induces the generation of C3a and C5a in a manner that bypasses the C3 and C5 convertases. To determine whether the generation of C3a and C5a was linked to the activation of the contact system, we next examined C3a and C5a generation in factor XII–depleted plasma (Fig. 4). As expected, zymosan induced the generation of C3a and C5a in factor XII–depleted plasma, and this activity was inhibited by EDTA. In contrast, neither C3a nor C5a was generated in factor XII–depleted plasma activated with OSCS, suggesting that OSCS bypasses the normal pathways for complement activation in a manner that is dependent on contact activation through factor XII. The generation of C5a could be restored by reconstituting the factor XII–depleted plasma with purified factor XII (Fig. 4A). This finding is further supported by the observation that C5a generation induced by OSCS-contaminated heparin can be inhibited by aprotinin, a protease inhibitor of kallikrein but not of factor XIIa (Fig. 4A). Crosstalk between the contact system and the complement cascade has been suggested previously.[15-18] For example, factor XII has been shown to activate the classical pathway by activating C1.[15] It has also been proposed to substitute for factor D in activating the alternative pathway.[16] However, in these cases, activation of the complement cascade still occurs through divalent cation–dependent pathways. Kallikrein has been shown to act directly on C5 to generate C5a-like biologic activity.[17] Both kallikrein and factor XII can activate the plasminogen pathway leading to the activation of plasmin, which has also been implicated in complement activation.[18] Preliminary data suggest that OSCS is unable to induce C5a generation in plasminogen-depleted plasma (data not shown).

To identify an appropriate species for in vivo testing of OSCS, a panel of plasma samples were screened for amidolytic activity in response to OSCS-contaminated heparin (Fig. 5A). Only swine plasma supported robust amidolytic activity of kallikrein in response to kaolin and OSCS-contaminated heparin but not control heparin. In contrast, rabbit, horse, and rat plasma showed moderate-to-robust amidolytic activity in response to kaolin but not to OSCS-contaminated heparin. These findings are consistent with a report that initial attempts to provoke an allergic response with suspect lots of heparin were unsuccessful.[8] Similarly, we found that rabbits treated with 5 mg of intravenous OSCS-contaminated heparin per kilogram showed no change in temperature, blood pressure, or heart rate as compared with rabbits treated with control heparin (data not shown). Wiggins[19] demonstrated previously that dextran sulfate can induce hypotension in rabbits, but only at a high dose (20 mg per kilogram) and in a manner independent of complement or kinin activation. In contrast, moderate doses of dextran sulfate (5 mg per kilogram) induced a robust hypotensive response in pigs that was dependent on activation of the contact system.[20]

Figure 5 (facing page). In Vitro and In Vivo Activity of OSCS.

Human, rat, rabbit, pig, and horse plasma samples were incubated with various concentrations of OSCS-contaminated unfractionated heparin (UFH) or control UFH (Panel A). Kaolin-containing buffer was tested as a positive control. Buffer alone was included as a negative control. Kallikrein amidolytic activity was assessed by the addition of the S-2302 chromogenic substrate; OSCS induces hypotension and kallikrein activity in swine (Panels B and C). Anesthetized Yorkshire crossbred pigs (three to six pigs per group) were treated with a single intravenous bolus (5 mg per kilogram) of control UFH, OSCS-contaminated UFH, chondroitin sulfate A, or synthetic OSCS. Representative data for the heart rate, the mean arterial pressure, the systolic blood pressure, and the diastolic blood pressure are shown (Panel B). EDTA-anticoagulated plasma was collected at baseline and at 5, 10, 20, 40, and 60 minutes after infusion of test samples (Panel C). OD denotes optical density.

To test the in vivo activity of OSCS, pigs were treated with a single intravenous dose (5 mg per kilogram) of OSCS-contaminated heparin, control heparin, synthetic OSCS, or chondroitin sulfate A and were monitored for 60 minutes. Animals treated with control heparin and those treated with OSCS-contaminated heparin showed similar anti-Xa activity during the entire 60-minute observation period (activity at 5 minutes, approximately 3 to 4 IU per milliliter) (Fig. 4 in the Supplementary Appendix). Animals treated with chon-


A
OSCS UFH
250 μg/ml
25 μg/ml
2.5 μg/ml
Control UFH
250 μg/ml
25 μg/ml
2.5 μg/ml
Kaolin
Buffer
Kallikrein Activity (OD450 nM)
2.5
2.0
1.5
1.0
0.5
0.0
Human
Rat
Rabbit
Pig
Horse
B
Heart rate
Mean arterial pressure
Systolic blood pressure
Diastolic blood pressure
Control UFH
OSCS UFH
Chondroitin Sulfate A
OSCS
Heart Rate (beats per min)
Pressure (mm Hg)
150
100
50
0
0
10
20
30
Minutes
C
Control UFH
OSCS UFH
Chondroitin sulfate A
OSCS
Kallikrein Activity (OD450 nM)
1.0
0.8
0.6
0.4
0.2
0.0
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
20
40
60
Minutes

droitin sulfate A or synthetic OSCS showed no anti-Xa activity. These results suggest that any anticoagulant activity of OSCS is mediated through a non–antithrombin III–dependent mechanism. Two of six animals treated with OSCS-contaminated heparin had at least a 30% drop in blood pressure over the first 30 minutes after infusion (Fig. 5B). One animal remained in a hypotensive state for more than 15 minutes. In contrast, none of the four animals treated with control heparin showed any substantive changes in blood pressure. The adverse events were more severe in pigs treated with the synthetic OSCS, a result consistent with the greater exposure to OSCS in animals treated with pure OSCS as compared with contaminated heparin containing approximately 20 to 30% OSCS. All three pigs treated with synthetic OSCS showed a profound drop in blood pressure (maximal decrease, 45 to 59%) and a concurrent increase in heart rate within minutes after infusion. One animal had difficulty breathing and became cyanotic after a precipitous drop in blood pressure. The heart rate of a second animal increased from 114 beats per minute to 196 beats per minute within 4 minutes after the infusion of OSCS. The third pig showed a transient but pronounced spike in heart rate with a corresponding drop in blood pressure (Fig. 5B). In contrast, none of the three pigs treated with chondroitin sulfate A showed any significant changes in blood pressure or heart rate within the first 30 minutes after drug infusion. Thus, intravenous infusion of OSCS is capable of recapitulating the hallmark cardiovascular features of the reaction in swine. The changes in physiological parameters were mirrored by rapid induction of the amidolytic activity of kallikrein (Fig. 5C). Kallikrein activity remained high throughout the observation period, even after the vital functions returned to normal, suggesting depletion of high-molecular-weight kininogen and inactivation of bradykinin by kininases in vivo, as previously shown with dextran sulfate.[20] Induction of kallikrein activity was evident in all animals that received OSCS-contaminated heparin, even when no substantive changes in blood pressure were observed. These findings suggest that activation of kallikrein does not always manifest as clinical symptoms, perhaps because of individual variation in control mechanisms that regulate bradykinin activity. Nonetheless, these results also suggest that swine may be an appropriate species in which to assess the potential consequences of OSCS contaminant in cardiovascular and dialysis models as well as in heparin-coated devices.

DISCUSSION

The recent reports of allergic-type serious adverse events in patients receiving heparin and the subsequent detection of widespread contamination have caused intense international concern about the safety of this essential drug. Urgent problems included an immediate and unknown risk to patients' lives, a threat to the supply of a widely used, essential drug, and the need for international cooperation in managing the integrity of a global supply chain. This crisis necessitated an urgent need to both understand the basis for these clinical events and to prevent future occurrences. The development of an analytic assay for OSCS, coupled with the rapid response of manufacturers and regulatory authorities around the world, has undoubtedly limited the harm. However, in the absence of a biologic link between the OSCS contaminant and the adverse events, the adequacy of screening heparin lots to prevent a recurrence is a concern.

Determining whether a link exists between the presence of OSCS and a biologic response required the convergence of two distinct analyses. First, there was a requirement to develop analytic techniques of sufficient sensitivity and specificity to ensure accurate identification and quantification of contaminants or impurities that are present within heparin. Second, there was a requirement to develop a sensitive, clinically appropriate biologic test to determine at what levels, if any, the OSCS would have relevant biologic activity.

With regard to the analytic techniques, a tiered approach was required to ensure effective translation to biologic characteristics. Screening methods were developed to rapidly identify whether heparin lots were contaminated or impure. Then, methods were further developed to enable quantification of the contamination levels. Finally, more sophisticated techniques, such as multidimensional NMR, enabled complete characterization of the contaminant or impurity. This tiered approach was necessitated by the fact that heparin is a polydisperse mixture of glycosaminoglycan chains; orthogonal techniques were therefore required to ensure capture of the other nonheparin components.

Here, we demonstrate that the OSCS present in suspect heparin lots, as well as a synthetic OSCS standard, can directly activate the contact system and induce the generation of C3a and C5a anaphylatoxins in vitro. Moreover, OSCS activates kallikrein in vivo and can induce a profound hypotensive response in pigs, thus providing a potential biologic link between the contaminant and the anaphylactoid reactions seen in affected patients. The finding that hypotension did not develop in all animals treated with OSCS-contaminated heparin, even at a relatively high dose, is consistent with the observation that the majority of patients who received contaminated heparin did not experience an adverse event. However, it is important to note that all animals treated with OSCS-contaminated heparin showed evidence of kallikrein activation in vivo, even in the absence of clinical signs. Patients undergoing dialysis who are also receiving heparin therapy are already at high risk for hypotension because of their exposure to the dialysis membrane, which can also activate the contact system, and their treatment with angiotensin-converting–enzyme inhibitors, which inhibit bradykinin degradation. Exposure to OSCS-contaminated heparin may further increase the risk and could potentially trigger an adverse event. Finally, these findings also suggest that a simple in vitro bioassay could complement the previously described analytic tests[4] to help protect the global supply chain of heparin, by allowing the screening of heparin lots for the presence not only of OSCS but also of other polysulfated contaminants that may have unintended pharmacologic consequences.

Supported by the National Institute of General Medical Sciences (grant GM57073, to Dr. Sasisekharan).

Drs. Kishimoto, Ganguly, Lansing, Zhao, Galcheva-Gargova, Roy, Shriver, and Venkataraman, Mr. Smith, and Mr. Baily reporting being employees of Momenta Pharmaceuticals and holding equity in the company, which has technology on the analysis and characterization of complex mixtures, including heparin. Drs. Sasisekharan and Langer report receiving consulting fees from Scientific Protein Labs and Momenta Pharmaceuticals and holding equity in Momenta Pharmaceuticals. Dr. Austen reports receiving consulting fees from Momenta Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

We thank Dr. Allen P. Kaplan for helpful discussions; Pete Jobst, Animal Resource Manager, and Andrea Aman, Animal Care Technician, at the Virginia–Maryland Regional College of Veterinary Medicine for their excellent technical help during the in vivo experiments; and Ms. Alison Long, Mr. Chris Honan, Dr. Cedric Hubeau, and the staff of the Massachusetts Institute of Technology Division of Comparative Medicine for help with the animal studies.

REFERENCES

1. Acute allergic-type reactions among patients undergoing hemodialysis — multiple states, 2007–2008. MMWR Morb Mortal Wkly Rep 2008;57:124-5.
2. Information on adverse event reports and heparin. Rockville, MD: Food and Drug Administration, 2008. (Accessed April 23, 2008, at http://www.fda.gov/cder/drug/infopage/heparin/adverse_events.htm.)
3. Information on heparin sodium injection. Rockville, MD: Food and Drug Administration, 2008. (Accessed April 23, 2008, at http://www.fda.gov/cder/drug/infopage/heparin/default.htm#screening.)
4. Guerrini M, Beccati D, Shriver Z, et al. Oversulfated chondroitin sulfate is a major contaminant in heparin associated with adverse clinical events. Nat Biotechnol (in press).
5. Hojima Y, Cochrane CG, Wiggins RC, Austen KF, Stevens RL. In vitro activation of the contact (Hageman factor) system of plasma by heparin and chondroitin sulfate E. Blood 1984;63:1453-9.
6. Henry SP, Giclas PC, Leeds J, et al. Activation of the alternative pathway of complement by a phosphorothioate oli-gonucleotide: potential mechanism of action. J Pharmacol Exp Ther 1997;281:810-6.
7. Silverberg M, Diehl SV. The autoactivation of factor XII (Hageman factor) induced by low-Mr heparin and dextran sulphate: the effect of the Mr of the activating polyanion. Biochem J 1987;248:715-20.
8. Baxter provides update on the heparin investigation. Deerfield, IL: Baxter, March 19, 2008. (Accessed April 23, 2008, at http://www.baxter.com/products/biopharmaceuticals/downloads/heparin_03-19-08.pdf.)
9. Silverberg M, Dunn JT, Garen L, Kaplan AP. Autoactivation of human Hageman factor: demonstration utilizing a synthetic substrate. J Biol Chem 1980;255:7281-6.
10. Verhamme IM, Bock PE, Jackson CM. The preferred pathway of glycosaminoglycan-accelerated inactivation of thrombin by heparin cofactor II. J Biol Chem 2004;279:9785-95.
11. Stead N, Kaplan AP, Rosenberg RD. Inhibition of activated factor XII by antithrombin-heparin cofactor. J Biol Chem 1976;251:6481-8.
12. Olson ST, Sheffer R, Francis AM. High molecular weight kininogen potentiates the heparin-accelerated inhibition of plasma kallikrein by antithrombin: role for antithrombin in the regulation of kallikrein. Biochemistry 1993;32:12136-47.
13. Pixley RA, Cassello A, De La Cadena RA, Kaufman N, Colman RW. Effect of heparin on the activation of factor XII and the contact system in plasma. Thromb Haemost 1991;66:540-7.
14. Kaplan AP, Austen KF. A prealbumin activator of prekallikrein. II. Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin. J Exp Med 1971;133:696-712.
15. Ghebrehiwet B, Silverberg M, Kaplan AP. Activation of the classical pathway of complement by Hageman factor fragment. J Exp Med 1981;153:665-76.
16. DiScipio RG. The activation of the alternative pathway C3 convertase by human plasma kallikrein. Immunology 1982;45:587-95.
17. Wiggins RC, Giclas PC, Henson PM. Chemotactic activity generated from the fifth component of complement by plasma kallikrein of the rabbit. J Exp Med 1981;153:1391-404.
18. Schaiff WT, Eisenberg PR. Direct induction of complement activation by pharmacologic activation of plasminogen. Coron Artery Dis 1997;8:9-18.
19. Wiggins RC. A different cleavage site for high molecular weight kininogen in vivo following intravenous injection of dextran sulfate in the rabbit. Circ Res 1986;58:595-604.
20. Siebeck M, Cheronis JC, Fink E, et al. Dextran sulfate activates contact system and mediates arterial hypotension via B2 kinin receptors. J Appl Physiol 1994;77:2675-80.

Copyright © 2008 Massachusetts Medical Society.

Mr. STUPAK. Thank you.

Mr. Strunce, for an opening statement, please.

STATEMENT OF DAVID G. STRUNCE, CHIEF EXECUTIVE OFFICER, SCIENTIFIC PROTEIN LABORATORIES, LLC, WAUNAKEE, WISCONSIN; ACCOMPANIED BY YAN WANG, PH.D., VICE PRESIDENT OF BUSINESS DEVELOPMENT AND RESEARCH, SCIENTIFIC PROTEIN LABORATORIES, WAUNAKEE, WISCONSIN.

Mr. STRUNCE. Chairman Stupak, Ranking Member Shimkus and members of the subcommittee, I am David Strunce, president and chief executive officer of Scientific Protein Laboratories.

I am accompanied by Dr. Yan Wang, vice president of business development and research for SPL and general manager of Changzhou SPL. Dr. Wang is an American citizen who holds a Ph.D. in chemistry and has worked in the pharmaceutical and fine chemical industry since 1993.

Our companies supply active pharmaceutical ingredients used by other manufacturers to produce finished drug products. SPL's facility in Waunakee, Wisconsin, has more than 150 employees and has been producing heparin sodium for more than 30 years with an exemplary regulatory record. Changzhou SPL has approximately 30 employees and has been producing heparin API since 2004.

SPL and Changzhou SPL are absolutely committed to producing drug ingredients of the highest quality. We are deeply concerned that a contaminant that has been identified in certain API products was made from Chinese crude. We have great sympathy and concern for any patient who has suffered adverse events potentially associated with heparin.

Our companies have cooperated fully in the FDA's investigation of the origin of the contaminant identified in heparin products around the world. And we have committed to testing all of our heparin products using the newly identified tests.

Let me make a few points.

First, the recent worldwide contamination appears to be the result of a deliberate act upstream in the supply chain. The contamination was not SPL- or Changzhou SPL-specific. The contaminant has now been detected in heparin products produced by a wide variety of manufacturers around the world, with no connection whatsoever to our suppliers.

Sophisticated new tests have shown that the contaminant was present in crude heparin before it ever reached SPL or Changzhou SPL. Unfortunately, the test used previously throughout the industry did not enable us or other manufacturers to detect the substance.

Second, we built the Changzhou facility to access the raw material supply needed to meet the world medical demand for heparin, not to save money. China is the world's leading producer of pigs, slaughtering about five times as many pigs as the U.S. The material from those pigs is absolutely necessary to meet the increasing medical need for heparin, both in the U.S. and other countries. Indeed, more than one-half of the finished heparin products in the United States and globally are made from Chinese-source material.

In addition, Chinese raw material is not inexpensive. At times, the cost of Chinese crude heparin has exceeded the cost of North American raw material.

Third, we built the Changzhou facility to U.S. and equivalent international standards, and it was registered with the FDA. As photos attached in my written testimony show, Changzhou SPL is a modern facility. We have been quite transparent with the FDA regarding the controls in place for our production chains in China.

We understand that the Committee is concerned that this Changzhou SPL facility was not inspected by the FDA before the 2004 approval of the Baxter supplemental NDA. However, Changzhou was fully available and prepared for an FDA inspection. Detailed information on Changzhou SPL quality control and manufacturing processes had been on file with the FDA since 2002. The Changzhou SPL facility also had been audited by third parties for GMP compliance.

At the time of the Baxter approval, we believed that the FDA was aware of and was satisfied with the quality systems that had been put in place.

As you know, FDA inspected the Changzhou SPL facility this past February, and we now have received a warning letter. As the agency has previously stated, there is no relationship between the inspectional observations referenced in the warning letter and the contamination which occurred upstream in the heparin supply chain. We strongly believe that the facility was in substantial compliance with then-current GMPs for heparin API, and we will provide a comprehensive response to the warning letter.

Finally, we are fully supportive of FDA's decision to increase its inspectional capabilities in China and applaud your efforts to provide the agency with additional resources for foreign inspection activities. We recognize that in spite of SPL's strong reputation for quality developed over decades, we, as well as others producing heparin products, must work to regain the confidence of the public. We pledge to continue to work with the FDA, Chinese authorities, and others to uncover the source of this contamination and take whatever steps are necessary to protect the public health.

Thank you for the opportunity to participate in today's hearing, and I look forward to addressing your questions.

[The prepared statement of Mr. Strunce follows:]

Statement of David G. Strunce
President and Chief Executive Officer
Scientific Protein Laboratories LLC

Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives

April 29, 2008

Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee, I am David Strunce, President and Chief Executive Officer of Scientific Protein Laboratories LLC ("SPL"). I am accompanied by Dr. Yan Wang, Vice President of Business Development and Research for SPL, and General Manager of Changzhou SPL Company, Ltd. ("CZSPL"), a Chinese joint venture company in which SPL holds a majority interest. Dr. Wang is an American citizen who holds a Ph.D. in chemistry and has worked in the pharmaceutical and fine chemical industries since 1993.

We are here today to provide you with our perspective on the issues that have been raised regarding heparin products of Chinese origin. We also hope to contribute to your consideration of the broader issues surrounding the inspection by the Food and Drug Administration ("FDA") of foreign drug manufacturing facilities.

We would first like to provide some background about SPL and CZSPL. SPL is a supplier of active pharmaceutical ingredients ("API") used by other manufacturers to produce and market finished drug products. Our manufacturing facility in Waunakee, Wisconsin has more than 150 employees. We have been producing heparin sodium USP API at the Waunakee facility for more than thirty years, with an exemplary regulatory record. SPL also holds a majority interest in CZSPL, a joint venture company in Changzhou City, China. CZSPL, which has just over 30 employees, has been producing heparin API since 2004.

SPL and CZSPL are absolutely committed to producing drug ingredients of the highest quality. We are deeply distressed by what appears to have been the intentional introduction of a synthetic contaminant into the crude heparin supply in China. As the Committee knows, the test methods used safely for many years in the heparin industry were incapable of detecting this substance in heparin API produced by SPL, CZSPL, or any other manufacturer of heparin API. As I believe you are also aware, both SPL and CZSPL have cooperated fully in the FDA's investigation of the root cause of the recent events. We are determined to do what we can to understand how this situation arose and to prevent similar events in the future. Of course, we have great sympathy and concern for any patient who has suffered adverse events potentially associated with heparin.

Background on Heparin Production

Heparin from porcine sources has been used in medical practice for decades, and it remains an important active ingredient in anticoagulant or blood thinning prescription drug products. Like certain other drug and biological products, the starting material for heparin is from a natural source. Specifically, the raw source material is derived from the small intestinal tissue of pigs. In the United States, SPL buys such raw source material from slaughterhouses and processing facilities located in the United States and Canada, and then processes those raw materials to make heparin API. The production process involves extracting heparin from the raw source materials into an intermediate form from which the purified heparin API is produced. SPL also produces certain API products in the United States starting with Chinese crude heparin. This material arrives as a dried granular substance on which certain preliminary processing steps have already been performed. In China, CZSPL produces heparin API from Chinese crude heparin.

The supply chain in China begins with the slaughtering of pigs at government-regulated slaughterhouses, which provide the intestines to casing/crude heparin workshops. The workshops then separate the intestines into casings and mucosa, process the intestinal mucosa into crude heparin, and provide the crude heparin to consolidators. In the supply chain, SPL and CZSPL purchase crude heparin from approved consolidators who combine the crude heparin obtained in smaller quantities from workshops. CZSPL and SPL then test the crude heparin, process and purify it into heparin sodium USP, and perform final testing, all under current good manufacturing practices ("GMPs") applicable to heparin API products. The resulting product is bulk, packaged heparin sodium that meets United States Pharmacopeia and similar international pharmacopeial standards, as well as the specifications of our customers. Such products are sold to manufacturers of finished pharmaceuticals, who then further process, test, package and sterilize the finished heparin products for distribution to their customers pursuant to specific FDA drug approvals.

We have attached to this testimony photographs of facilities in the SPL and Changzhou SPL supply chains in China. As you can see from these photographs, our supply chain is quite different from the uncontrolled conditions depicted in the media.

Heparin raw materials are not sourced in China simply in order to access cheaper starting material. Indeed, at times, the price of Chinese crude heparin has exceeded the cost of North American raw material. However, the global medical demand for heparin products has increased dramatically over the last decade, and there is an insufficient supply of pigs in North America to satisfy that demand. China is the world's leading producer of pigs, slaughtering about five times as many pigs per year as the United States. The material from those pigs is necessary to meet the increasing medical need for heparin both in the United States and other countries around the world. More than one-half of finished heparin products in the United States and globally are made from Chinese source material.

Quality Controls and Regulatory Compliance by SPL and CZSPL

The SPL and CZSPL facilities are registered as drug manufacturers with the FDA, and the heparin sodium USP API products produced by SPL and CZSPL for commercial distribution in the United States are listed with the Agency. Both the SPL and CZSPL API products are the subject of drug master files ("DMFs") submitted to the Agency, which detail the manufacturing and quality control processes that SPL and CZSPL use in producing heparin sodium API from Chinese crude heparin. These DMFs are updated at least annually, and are referenced by our customers as part of their drug applications. SPL and CZSPL have been open and transparent with FDA regarding the specific controls in place for our various production chains, including the use of Chinese source materials.

Like SPL, the CZSPL facility in China was designed and engineered to manufacture heparin sodium USP under conditions meeting United States current GMP requirements (as well as equivalent international standards) for API products. CZSPL produces the materials in modern facilities using modern equipment and methods, and employs qualified personnel who are trained and experienced in United States quality system principles.

At both facilities, efforts to ensure the quality of heparin API are extensive. Neither SPL nor CZSPL accepts crude heparin from Chinese suppliers on faith. Heparin quality controls begin with controls over sourcing and collection to assure that the porcine material is appropriately derived and processed. For more than a decade, SPL has conducted on-site audits of the crude heparin consolidators in China from whom we receive crude heparin. SPL obtains samples of crude heparin from each consolidator and manufactures test batches of heparin USP API using those sample materials to ensure the quality of the incoming materials. All of this work is done before approving a consolidator as a crude heparin supplier to SPL and CZSPL. SPL and CZSPL also maintain purchasing orders with each raw material supplier and our dealings with those parties are fully documented.

SPL and CZSPL have worked with the FDA in taking proactive measures to increase quality controls over Chinese crude heparin, even in the absence of any known problems with the quality of those materials. While it may seem ironic today, part of SPL's rationale for engaging in the CZSPL joint venture was to facilitate our ability to monitor Chinese crude heparin suppliers. Thus, for example, during 2006, well before there had been any news of blue ear virus in pigs or contaminated heparin, CZSPL established and implemented a process of auditing and individually approving the crude heparin workshops that supply material to the consolidators from whom CZSPL obtains crude heparin.

Recent Heparin Concerns

As you know, in January 2008, Baxter International initiated a recall of certain lots of finished heparin products manufactured using API produced by CZSPL. Subsequently, SPL announced our own recall of Chinese-sourced heparin API sold to other customers. It is important to note that, based upon extensive testing to date, only specific lots of heparin produced during 2006 and 2007 from Chinese crude heparin were subject to these recalls. SPL heparin API products produced solely from North American source materials have not been affected.

On March 19, 2008, FDA announced that it had identified a suspected contaminant known as oversulfated chondroitin sulfate in certain finished heparin products. SPL and CZSPL cooperated fully and proactively in FDA's scientific efforts to study the substance, including by identifying and making available leading academic experts. There remain many unanswered questions about the origin of this substance and how it was introduced into the crude heparin supply chain in China.

It has now been publicly reported that oversulfated chondroitin sulfate has been found in heparin products around the world, most of which are completely independent of our supply chain. This information, together with our internal testing, makes clear that the substance in question was present in the crude heparin material before it ever reached the SPL or CZSPL production processes. Rather, the evidence suggests that the contamination occurred at some point in the supply chain upstream from API manufacturers. Unfortunately, as the FDA has made clear, due to the nature of the suspected contaminant, current GMPs in the heparin industry and pharmacopeial testing standards, including potency testing and purification processes, could not detect, identify or remove the substance.

FDA recently designated two sophisticated methods -- proton nuclear magnetic resonance ("NMR") and capillary electrophoresis ("CE") -- as useful in detecting the presence of oversulfated chondroitin sulfate. At the time of the release of the products that have now been recalled, however, these specific methods for detecting oversulfated chondroitin sulfate had not been required or even identified by FDA, the USP, or foreign pharmacopeial bodies. Nor were these tests used within the industry. Unlike ordinary chondroitin sulfate, which is a naturally occurring component of heparin, the oversulfated form is not found in nature. Only the sophisticated new tests, developed after weeks of inquiry by scientists at the FDA and academic laboratories, have been able to detect the specific "peaks" relating to the oversulfated contaminant.

Using these tests, we recently tested reserve samples of incoming crude heparin from Chinese sources. Those samples showed "peaks" indicating that oversulfated chondroitin sulfate was present in certain batches of crude heparin before they reached SPL and CZSPL. Again, these NMR and CE test results are consistent with the other evidence that shows that any contamination with oversulfated chondroitin sulfate occurred at a point in the supply chain upstream from SPL and CZSPL.

Going forward, SPL and CZSPL have committed to the FDA that we will not release heparin products without employing these two new tests. Should further information suggest the advisability of other enhancements to practices, processes, or testing among heparin API producers, we will work with the FDA and other regulatory authorities to implement such changes.

Inspection of the CZSPL Facility

We understand that the Committee is concerned that the CZSPL facility was not inspected by the FDA prior to the 2004 approval of the Baxter supplemental NDA permitting sourcing of heparin API from CZSPL. CZSPL is not aware of FDA's internal handling of this issue. From our perspective, the CZSPL facility was fully available and prepared for an FDA inspection. SPL discussed the Changzhou joint venture with FDA field personnel as early as 1999, and formally notified FDA of the CZSPL joint venture in March of 2000. The DMF detailing the quality control and manufacturing processes for heparin API produced at the CZSPL facility was submitted to the Agency in 2002. Upon learning that FDA had approved Baxter's supplemental NDA authorizing it to manufacture and ship finished heparin products produced from CZSPL-supplied API, we assumed that FDA was aware of and was satisfied with the quality systems that had been put in place at CZSPL.

The CZSPL facility also has been subject to audits by various third parties to determine compliance with current GMPs and other manufacturer specifications. Such audits, like most thorough GMP audits, recommended certain improvements, which were implemented. However, these audits concluded that CZSPL's systems were GMP-compliant.

As you know, FDA inspected CZSPL in February 2008. After an extensive five-day inspection, FDA issued a list of observations, known as a Form FDA 483. On the day before Commissioner von Eschenbach's testimony before this Subcommittee a week ago, FDA issued a Warning Letter that repeated some of the observations from the 483. There is no relationship, however, between the FDA observations and the contamination of certain heparin sodium lots with oversulfated chondroitin sulfate. As the FDA and leading academic researchers have made clear, that substance simply was not detectable using then-existing testing methods for heparin. With all due respect to FDA, we believe that the CZSPL facility was and remains in compliance with United States and international current GMP and industry standards for a heparin API manufacturer, and that its products met and meet applicable pharmacopeial testing requirements, as well as additional customer specifications. On March 17, 2008, CZSPL submitted its response to FDA's 483, outlining in detail the steps it has taken and will take to address FDA's observations. A number of those activities are now completed. We are diligently pursuing completion of the remaining items, and we will be providing a comprehensive response to the Agency's Warning Letter.

SPL and CZSPL are fully supportive of FDA's mission. We support FDA's intention to place permanent inspectional staff in China, and applaud your efforts to provide the Agency with additional resources for foreign inspectional activities. Indeed, we believe such resources will ensure the maintenance of high standards across the industry and enhance the confidence of patients in an increasingly global drug supply environment.

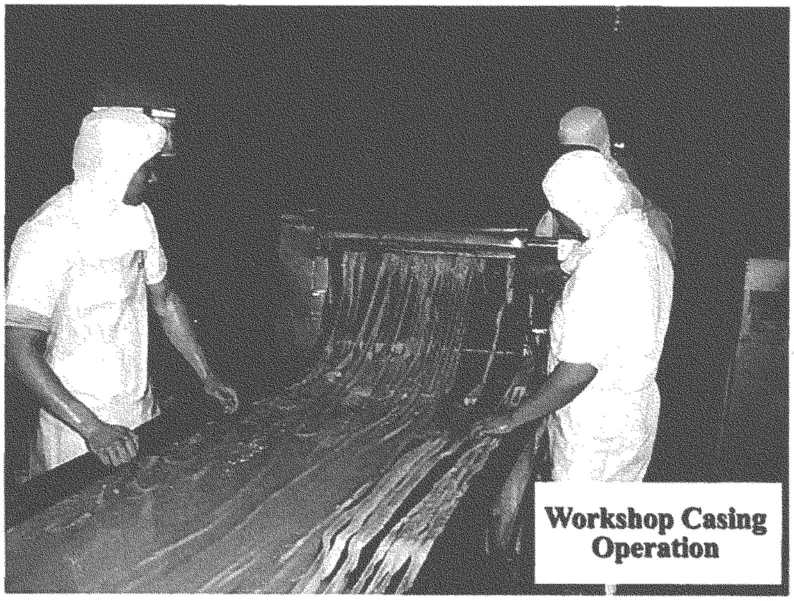
Conclusion

In closing, we know that in spite of SPL's strong reputation for quality developed over decades, we – as well as others producing heparin products - must work to regain the confidence of the public. The quality and safety of our API products is our central concern, and we will take whatever steps are necessary to protect the public health. In particular, we will continue to work with regulatory authorities in the United States, China, and other jurisdictions to uncover the source of the contamination and implement new controls to guard against future events of this kind.

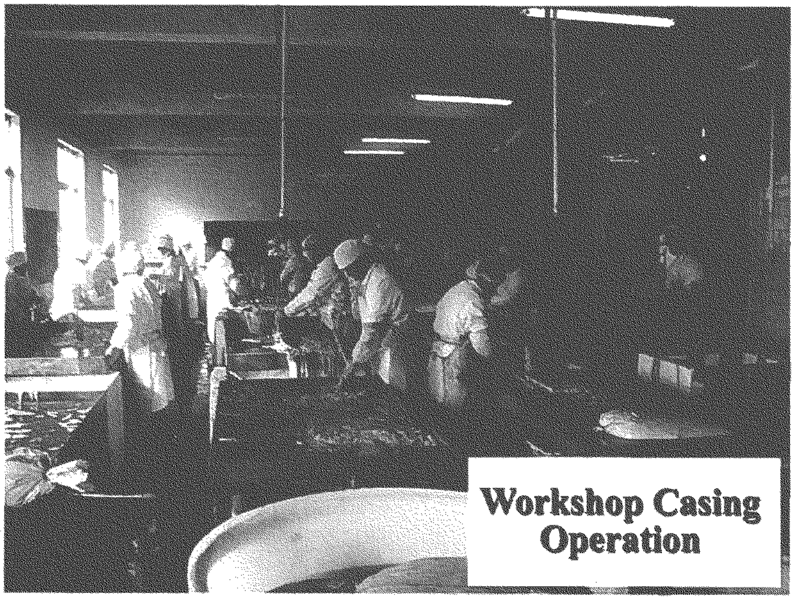
Mr. Chairman, Ranking Member Shimkus, and Members of the Subcommittee, thank you for the opportunity to participate in today's hearing. We understand your interest in these important issues, and we look forward to answering your questions.

PHOTOS OF CRUDE HEPARIN/CASING WORKSHOPS

Crude Heparin/Casing Workshops



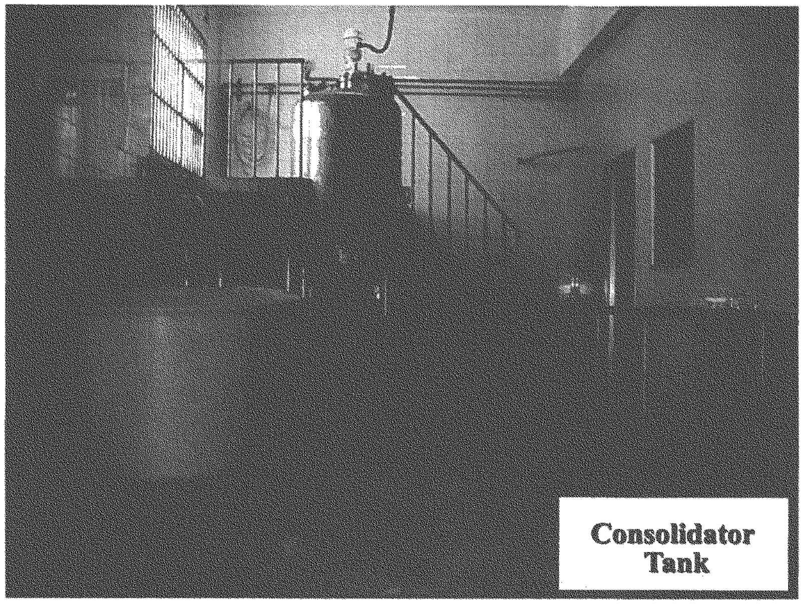
Workshop Casing Operation



Workshop Casing Operation

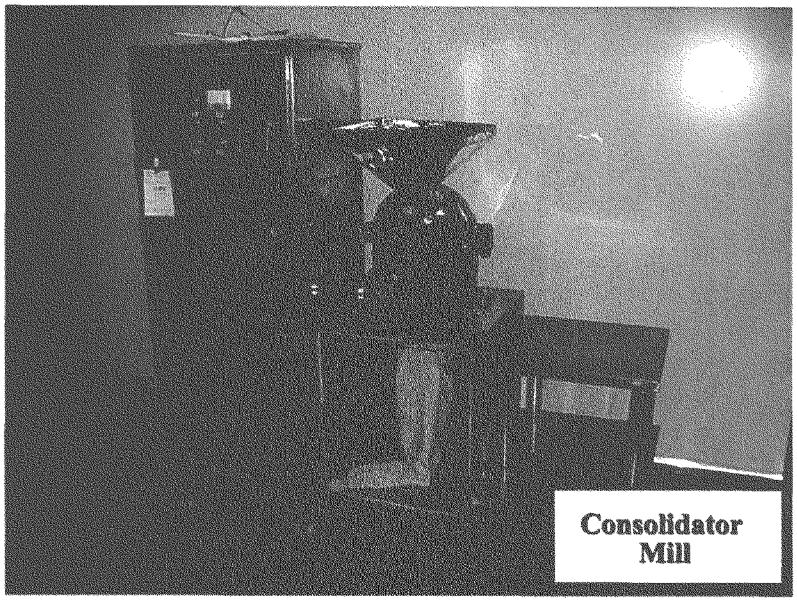
PHOTOS OF CONSOLIDATOR PLANTS

Consolidator Plants

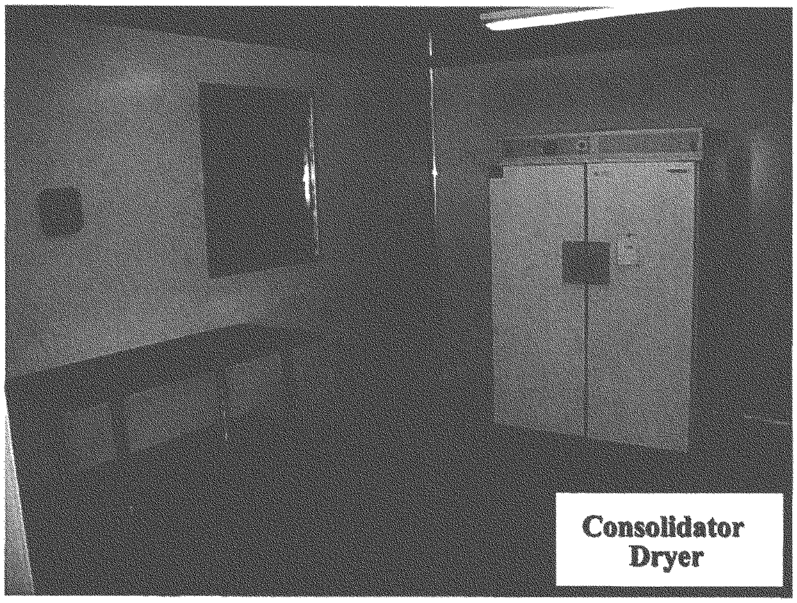

Consolidator
Tank

Consolidator
Plant

Consolidator Plants

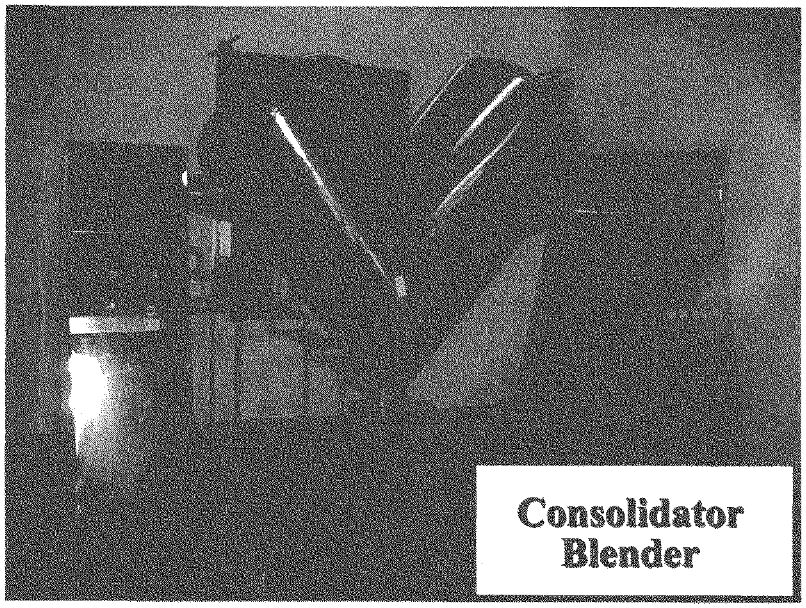


Consolidator Mill



Consolidator Dryer

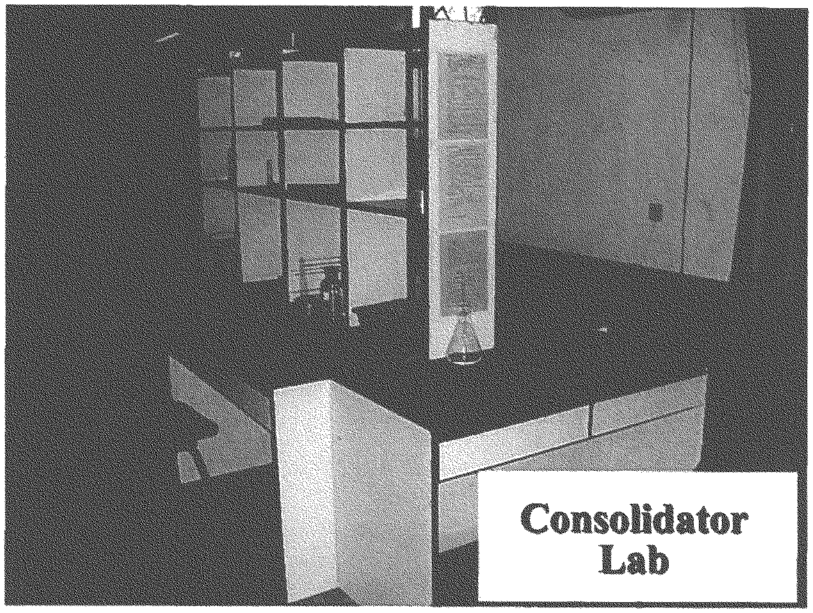
Consolidator Plants



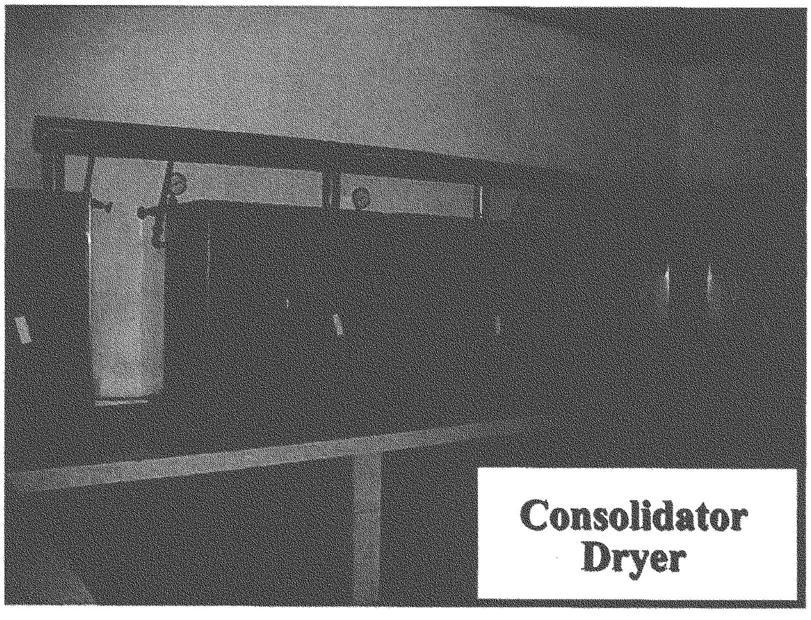
Consolidator Blender

Consolidator Mill

Consolidator Plants

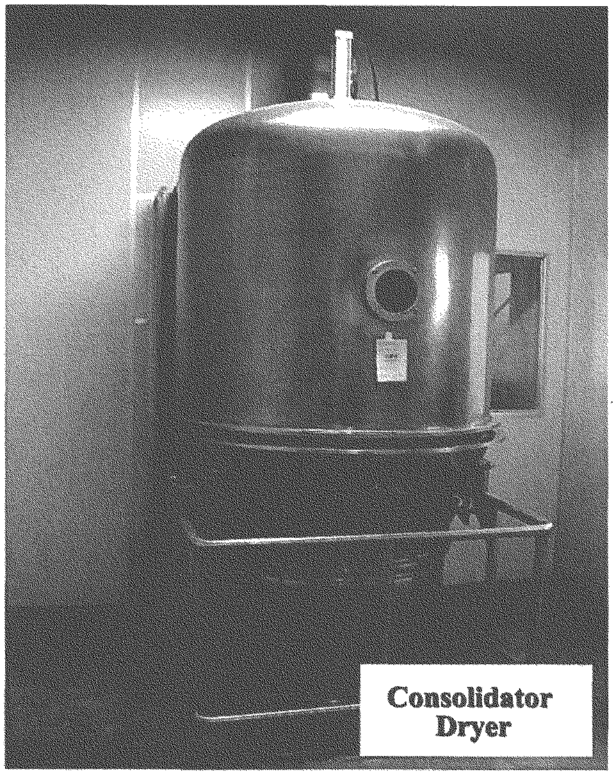


Consolidator Lab



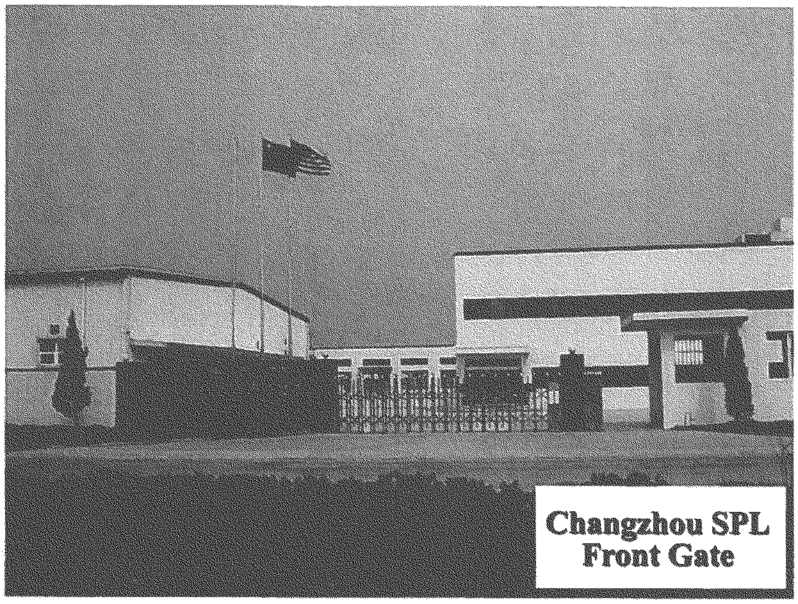
Consolidator Dryer

Consolidator Plants

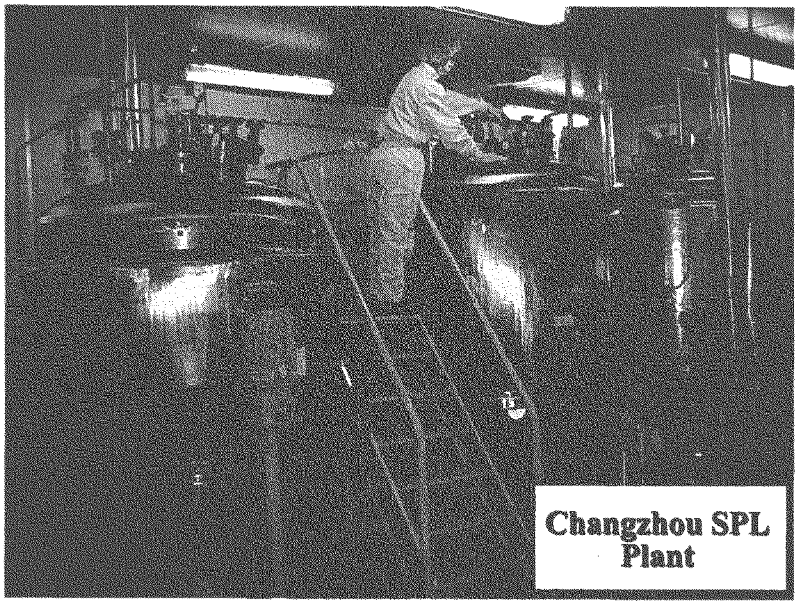


PHOTOS OF
CHANGZHOU SPL PLANT

Changzhou SPL Plant

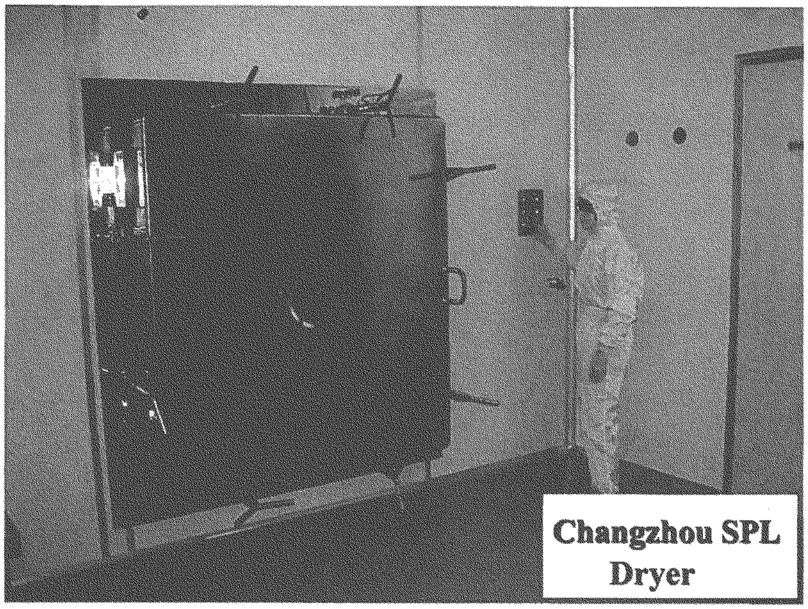


Changzhou SPL Front Gate

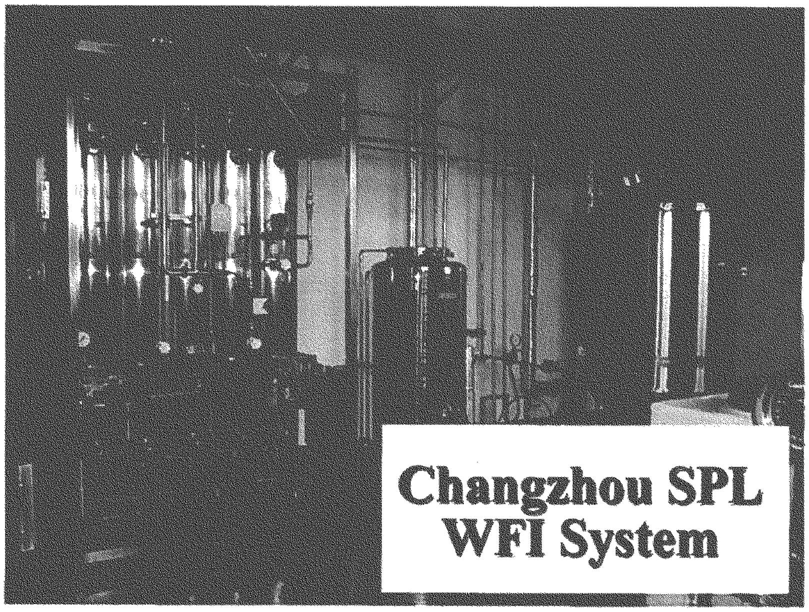


Changzhou SPL Plant

Changzhou SPL Plant

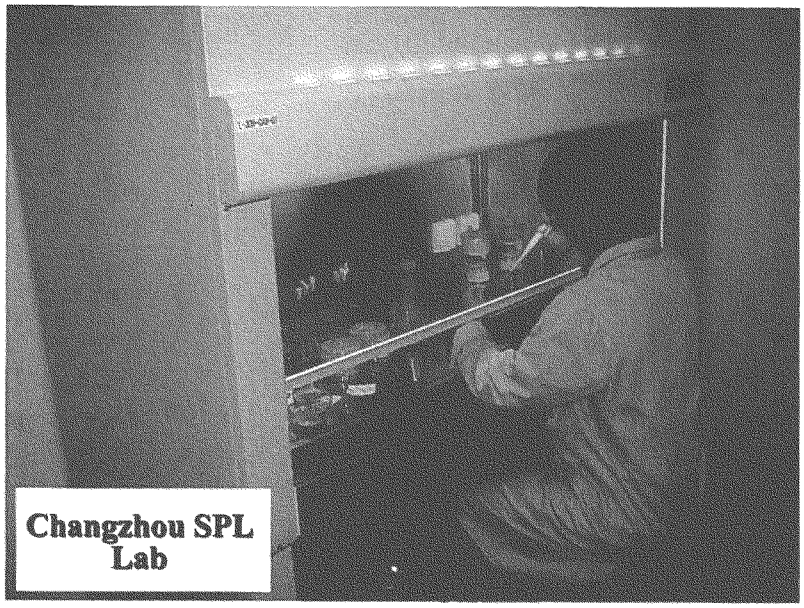


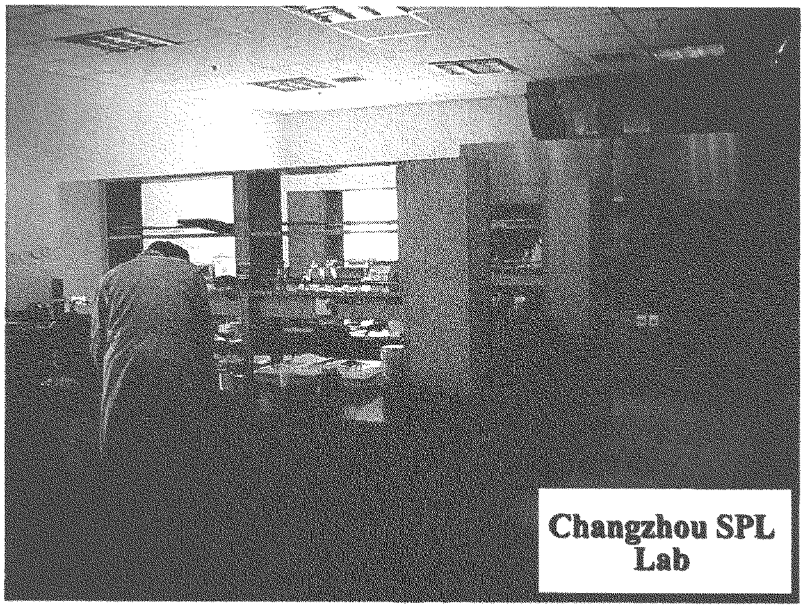
Changzhou SPL Dryer



Changzhou SPL WFI System

Changzhou SPL Plant





Mr. STUPAK. Thank you.

Dr. Wang, do you wish to testify?

Dr. WANG. I don't have an opening statement.

Mr. STUPAK. OK, thank you. We'll turn to questions.

Mr. Parkinson, right in there, in that big black book there, is our exhibit book. I asked earlier of Mr. Nelson, Exhibit No. 31. And this is a letter from Baxter to Changzhou SPL dated February 26, 2008. And I think it's the first page there of that exhibit. This letter states that Baxter's audit observations quote, "have been satisfactorily addressed," end of quote, and that Baxter is pleased to inform Changzhou SPL that the audit had been, in quotes, "closed."

Coincidentally, on that day FDA was finishing up its inspection of Changzhou SPL. By this time, Baxter was aware of the outbreak of heparin problems, was aware the FDA inspection team was in the Chinese plant, and was aware that the facility might have caused a role in this heparin outbreak.

In light of these facts, why did you close the audit on the plant that's possibly responsible for the contaminated heparin?

Mr. PARKINSON. Well, I can't speak to the exact chronology, Mr. Chairman, in terms of when this letter was sent versus learning of the actual initiation.

Mr. STUPAK. The date is on the letter right there, isn't it, February 28th?

Mr. PARKINSON. Well, our letter is dated February 26th.

Mr. STUPAK. The 26th, okay.

Mr. PARKINSON. But you cited the date of the FDA?

Mr. STUPAK. Finished up February 26th, right.

Mr. PARKINSON. Yes. And so the exact time during the day and what we knew at what time during that day I'm not sure what the exact chronology was during that period of time.

Mr. STUPAK. But even knowing all these problems, I mean you knew in January we had a problem with heparin. You even knew before that, you actually knew in the fall, didn't you, after St. Louis Children's Hospital, when their dialysis reported the problems?

Mr. PARKINSON. Yes, we knew the adverse events started to increase late in December, and obviously there was a lot of activity on this subject that took place.

Mr. STUPAK. Sure. So December, January, late February, 3 months later you're closing the audit because everything is satisfactory?

Mr. PARKINSON. Well, the audit that was performed in September was what was referred to as a routine inspection audit. I think a very different orientation than an inspection for cause, which was really the nature of the FDA inspection subsequent to the events that transpired. I'm not sure that we learned anything in terms of the adverse events on the product, and so on, that would have said at that point we're going to go back and change our inspection, change the observations.

Mr. STUPAK. Well, let me ask you this. The exhibit right in front of you, Exhibit No. 30, which I asked a number of questions on.

Mr. PARKINSON. No. 30?

Mr. STUPAK. Thirty, Exhibit No. 30. That's your September 2007—Baxter performed a good manufacturing audit of Changzhou, is that correct?

Mr. PARKINSON. Under 30 was the audit report; 31 is when we thanked them for the response.

Mr. STUPAK. OK. And you can go to the third page if you want. That's the audit, this is a report from that audit, right?

Mr. PARKINSON. Yes. With the observations you mean, the site of the observations?

Mr. STUPAK. Right. Now, you're aware that the FDA had never approved this plant for manufacture of heparin, right?

Mr. PARKINSON. We were aware of that, yes.

Mr. STUPAK. Didn't you have a responsibility to tell the FDA that this plant had never been inspected?

Mr. PARKINSON. We did communicate that to the Agency.

Mr. STUPAK. When, after?

Mr. PARKINSON. October of 2003, I believe.

Mr. STUPAK. So you told the FDA in October of 2003 this plant had never been inspected by the FDA, is that correct?

Mr. PARKINSON. Yes.

Mr. STUPAK. Did you, once you told the FDA that did they give you permission then to ship a product to the United States made out of that plant that had never been inspected?

Mr. PARKINSON. We received approval. We subsequently submitted our——

Mr. STUPAK. You received approval in what form, written form?

Mr. PARKINSON. Written form, yes.

Mr. STUPAK. Do you have that with you, do you have that written form with you?

Mr. PARKINSON. I don't have it right here.

Mr. STUPAK. If you could provide that to the Committee.

Mr. PARKINSON. We would be happy to do that. We actually submitted the prior approval supplement in February of 2004, I believe, and received the approval 4 months later, and we have written approval of that.

Mr. STUPAK. All right. So even though it was not inspected you felt you had no more responsibility to make sure the plant was inspected by the FDA then?

Mr. PARKINSON. After informing the FDA what additional responsibility we had relative to the FDA inspecting, I think, is a matter for discussion. Our broader responsibility, which we shoulder, is the quality of the product which we ensure is maintained in several different ways, not only instructions.

Mr. STUPAK. Sure. But I said in my opening statement I thought both Baxter and SPL had some responsibility here.

Mr. PARKINSON. Absolutely.

Mr. STUPAK. You are both companies that have been around for 75 years. You know before you ship a drug or even produce a drug here in the United States, the plant has to be pre-approved by the FDA, right?

Mr. PARKINSON. Right.

Mr. STUPAK. And it wasn't done here. So it seemed like that basic first rule was sort of ignored.

Mr. PARKINSON. That implies that we depend upon the FDA to ensure the quality of our product.

Mr. STUPAK. Right. But don't you also depend upon the FDA to assure you that you have that right, if you will, actually the privilege not a right, it's a privilege to sell drugs in the United States?

Mr. PARKINSON. Yes, it is.

Mr. STUPAK. And therefore doesn't that pre-approval—that pre-inspection approval gives you that, grants you that privilege?

Mr. PARKINSON. When we receive the approval for that supplement that we submit, yes, that gives us that privilege to do that.

Mr. STUPAK. Well, in your audit report it states the purpose of the audit was to, quote, "verify the effectiveness of Changzhou SPL's quality systems and technical capabilities with regard to applicable Baxter and regulatory requirements," isn't that correct?

Mr. PARKINSON. Yes.

Mr. STUPAK. OK. It appears that the audit then, this audit, it says in there, again I'm quoting now, "consistent of an in-depth review of Changzhou's quality systems and capabilities and included documentation and procedures related to incoming materials, sampling procedures to build the operations, quality assurance process, and stability operations," isn't that true?

Mr. PARKINSON. Yes.

Mr. STUPAK. Well, it appears that the audit found only one major observation related to the good manufacturing processes. Further, it appears that Changzhou SPL was approved to supply heparin API to Baxter as long as it addressed that one problem. In essence, the audit found that Changzhou SPL was capable of meeting good manufacturing products, process, right?

Mr. PARKINSON. That was our assessment.

Mr. STUPAK. OK. But then, yet 5 months later the FDA found Changzhou was incapable of meeting good manufacturing products, or practices, good manufacturing practices. FDA's inspection found major problems with the facility while your audit found only a handful of deviations, most of them apparently minor. In fact, FDA found so many problems that it's been barred—that it has barred products from Changzhou SPL from entering the United States. Why did the results of your two audits differ so much?

Mr. PARKINSON. Well, I can only speculate they were a different point in time. Each audit is obviously a snapshot in time. As I said a minute ago, ours was a routine audit that was initiated prior to any of these events having transpired, and the FDA's was one that was for cause. Knowing all the events that had transpired, I believe they had at least two individuals there for a number of days. As was cited earlier, we had an individual there for a day. One can argue, discuss, debate, perhaps, how much time is necessary. There is a correlation in my experience in the industry that the longer auditors, investigators spend in the facility the more things that they will find. I think it was a different point in time in a different context.

Mr. STUPAK. What changed in 5 months then between—what would change in your manufacturing process, anything change?

Mr. PARKINSON. I can't respond specifically to what changed in the manufacturing process from our inspection.

Mr. STUPAK. Well, were there changes between your inspection and the FDA inspection?

Mr. PARKINSON. I don't know. I've read the reports, but I don't know that I can ascertain from that whether or not there were specific changes that took place in that period of time.

Mr. STUPAK. So, well, if there's no change in your manufacturing process and there was no problems with heparin coming out of this plant prior to late '07, how did the chondroitin get into the heparin then?

Mr. PARKINSON. Well, I've listened to the testimony throughout the day, Mr. Chairman. And again this is speculative, and the working hypothesis I believe is that it didn't enter the supply chain in this particular facility that we're discussing, the audits. I would suggest to you, and the Committee, I think more frequent audits are a good thing. I think more in-depth audits are a good thing. We instituted as a company a policy in 2006 to do more frequent audits of our vendors. Those are good things to do.

Mr. STUPAK. Sure, they're good things to do. Will you help pay for them then or should the taxpayers pay for them, these inspections?

Mr. PARKINSON. Our own internal inspections of our own facilities?

Mr. STUPAK. No, the FDA inspections. I know you don't depend on the FDA inspections you said, so——

Mr. PARKINSON. Look, I am open minded. Well, first of all, I would say I think the FDA should do a comparable level of intensity of inspection in all facilities regardless of where they are in the world, okay. And we understand that requires a ramp-up of activity. Now you're asking the question about financing that, and it's the notion of users fees and so on. We're open-minded and receptive to that, okay, and we would like to work with the committee to move forward to discuss the specifics that might be associated with that.

Mr. STUPAK. Very good. Mr. Strunce, let me ask you this. If this plant in Changzhou is operating, there's never any problems until late 2007, and then suddenly we have this problem with the chondroitin, how did the chondroitin get into the substance? If it wasn't Baxter's responsibility, how about you guys?

Mr. STRUNCE. Well, Mr. Chairman, it seems to me that most of the evidence that we've heard, the testimony we've heard and the testing that has been done on finished product, on API, and on crude heparin and the fact that this contaminant has been found all over the world in supply chains that are completely separate from SPLs, it's clear to me that it entered upstream from Changzhou SPL and consequently the time period of the end of '07 is about the time period when it started to come through, which was undetectable by the analytical methods used in the industry at the time.

Mr. STUPAK. OK. So if it came from upstream, it had to come from the workshops, the consolidators, or someone before it got to your plant, is that what you're saying?

Mr. STRUNCE. That's correct, sir.

Mr. STUPAK. Well, in your written testimony you state that part of your rationale for entering into a joint venture in China was to facilitate your ability to monitor Chinese crude heparin suppliers. So if you're monitoring your Chinese crude heparin suppliers, how did the contamination, how did the chondroitin get in the heparin then, if you're monitoring it? That's one of your reasons for going to do business over there, so you can monitor your suppliers.

Mr. STRUNCE. That's absolutely true, and we were monitoring our suppliers.

Mr. STUPAK. Well, then what broke down? If you're monitoring and it still gets in, what happened?

Mr. STRUNCE. Well, monitoring is not exactly the same thing as living in the facility. We do routine audits of our workshops and of our consolidators. And the fact that this showed up in all of the supply chains coming out of China indicates that it was a very insidious act that attacks the supply chain of most companies producing heparin.

Mr. STUPAK. So if it attacked most companies, you're the only company being restricted for export to the United States?

Mr. STRUNCE. We're being restricted, but even that's not necessary because we wouldn't ship it anyway unless it were tested.

Mr. STUPAK. Do you think other manufacturers in China should be restricted for their heparin in the United States until we get this chondroitin supply issue resolved as to which one of the suppliers caused the problem here?

Mr. STRUNCE. No. My strong suggestion is that everybody that makes heparin at any level, from API to finished product, should be using these sophisticated tests that have been developed now before releasing any product. That's certainly what we've volunteered to do for the Agency, and we feel that everybody else should be doing that too. And in fact, we know that most companies around the world are not only testing the products that they have on the market, but are also testing their inventories.

Mr. STUPAK. But you can't, even if you did the testing you still can't reopen until you get reinspected, right?

Mr. STRUNCE. That's correct.

Mr. STUPAK. Because of good manufacturing practices that the FDA did not approve of?

Mr. STRUNCE. They——

Mr. STUPAK. Could the good manufacturing practices in any way contribute to the chondroitin getting into the heparin?

Mr. STRUNCE. I'm sorry, sir, could you repeat that?

Mr. STUPAK. Could your lack of good manufacturing processes—okay, could that, because you did not have good manufacturing processes at this plant according to the FDA, even though your audits say they're good, could that manufacturing process have somehow interjected chondroitin into this heparin?

Mr. STRUNCE. Absolutely not.

Mr. STUPAK. It has to be intentionally put in by a supplier somewhere, right?

Mr. STRUNCE. It seems to us that it's an intentional act upstream in the supply chain.

Mr. STUPAK. And you have no idea where?

Mr. STRUNCE. We don't know specifically where.

Mr. STUPAK. Mr. Shimkus for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. And I appreciate the chairman of the committee, and I think, Mr. Strunce, your last response is that that's what we're trying to find out. I know that's what industry wants to find out, I know that you all want to find out. I know, Mr. Parkinson, that Baxter is a household name, especially in the health care arena. I don't know if individual households, but because of the products you produce. SPL is not. Damage that can be done to the individual lives. And our first panelists are still here just like you were here, and which I appreciated. But of course, there is great damage done to the Baxter name, and it's important for a lot of reasons that you don't sell a product that's faulty. I mean, that's on anything and any manufactured goods.

You all sat through the other panels. And the last panel, I would just like to get a generic comment, the FDA, basically the committee, and I think the committee as the whole committee, and I think the FDA, at least at some level, realize that we need to do, from our end, more frequent inspections, that there may be some penalty regime established, there will be a questioner who pays. We'll probably work through this. A U.S. company is already paying income taxes to fund the Federal Government, but what about those companies that aren't U.S. incorporated companies, and there's the debate of the user fee or how else we may deal with this.

We do know that we also have to improve the FDA's real-time information flow through information technology, and those of you in the business sector have dealt with that on your own already.

What are your comments based upon the responses of the second panel on reforms? You were touching on it with Chairman Stupak a little bit where you would be open. Where would you like to see the Federal Government move and the FDA to be a partner in ensuring this? And that's the user fee debate, that's expansion of authority, and the like.

Mr. PARKINSON. Well, there's a lot of—it's a great question. There's a lot of dimensions to that. As I said, we support more inspections. Funding should be made available to allow the FDA to do more inspections. The source of that we can debate and discuss. I think it is important for the committee to appreciate that, while that's a good start, that's only one dimension of several aspects of what it's going to take to really fundamentally make a difference to enhance safety of the supply of medical products and pharmaceuticals.

The prior committee, to your question, commented on the need to invest in IT. The information systems are woefully lacking and need support. I also think the Agency should consider, and we would be happy to work with them, as I'm sure others in the industry would, to really implement something going forward that we recently implemented within Baxter as a result of this tragic experience, which is to dedicate a group of Ph.D.s and scientists to, not unlike the law enforcement agencies, try to think like the bad guys.

Mr. SHIMKUS. And you're referring to this whole threat evaluation?

Mr. PARKINSON. Absolutely.

Mr. SHIMKUS. And was this incident really the first wake-up call to move in that direction?

Mr. PARKINSON. It's a matter of degree, but I think it's the first time that Baxter has proactively established a resource.

Mr. SHIMKUS. The other important thing is, about this approach, is, following up on what Dr. Burgess said earlier, or even some other, and what if this was an intentional use of science and technology to adulterate a common chemical use, slip through the investigation regime, and we would need in essence a credible threat response operation from industry and government to be engaged.

Mr. PARKINSON. But frankly that's the way we need to think, whether it's due to economic motivations, terrorism, that's the new world and that's the orientation.

Mr. SHIMKUS. So as we move on a process to authorize reforms in the FDA followed up hopefully by the appropriate funding, that we ought to probably get that right with this threat focus?

Mr. PARKINSON. I think that's right, and I think the E Pedigree Initiative is an important part of that as well.

Mr. SHIMKUS. Mr. Strunce, you indicate that the cost of heparin was not a principal reason for locating your facility in China, is that correct?

Mr. STRUNCE. That's correct.

Mr. SHIMKUS. While the cost of heparin was not a factor for SPL, do you think it plays a role in the incentive among somebody in China to cut the supply with counterfeits?

Mr. STRUNCE. Well, when the counterfeiting appears to have happened at a time when the price was rising for Chinese heparin, it was rising dramatically and is still very high. So in answer to your question I believe that that provided some additional incentive. There was less material available because there were several factors that impacted the shortage of material, which is what drove up the price. So it provided, perhaps, the incentive for someone to use these measures.

Mr. SHIMKUS. Tell me again a size difference between the Wisconsin facility and the facility in China.

Mr. STRUNCE. We have——

Mr. SHIMKUS. Can we compare, I mean, is there an easy way to compare the almost duplicate models, only changes in size?

Mr. STRUNCE. They're pretty close, but the SPL in Wisconsin has about 150 employees. They produce basically two products: pancreatin and heparin, both from animal source. The facility in China produces primarily only heparin, produces about, I guess about maybe one-fifth of the overall capabilities of the SPL facility.

Mr. SHIMKUS. So it's quite a bit smaller operation?

Mr. STRUNCE. It's smaller. Yes, it is.

Mr. SHIMKUS. Mr. Wang, the FDA inspection of one heparin consolidator quoted the owner to say that his firm has consistently been unable to meet SPL's production needs because there is not enough crude heparin available. He said the number of pigs slaughtered in China had dropped by 200 million since 2005. If SPL was aware of this supply crunch, what did you do to ensure the quality of supply?

Dr. WANG. In 2007, we actually reduced our production because the demand cannot meet our need.

Mr. SHIMKUS. Were you concerned about adulteration of the commodity product?

Dr. WANG. Yes, we are always on the lookout. At that time in 2007, because of the price increase in heparin, we are always mindful of potential contamination for economic interest. And the major thing we look at, and also the industry is looking at, is probably cheaper heparin from other species. So in 2007, we're putting a test method, a very sensitive test method called PCR, in order to distinguish the porcine-based heparin from other sources.

Mr. SHIMKUS. I've tried to talk to my colleagues about trying to understand the input and the outputs and the quality assurance on both ends of the manufacturing arena, making sure that the product coming in is up to the standards required and the quality out. I think that's the frustration here with the inspection regime. Because the tough thing for public policy people, whether there was deception imposed by additives that mimicked the test results, the reality is we didn't have people walking around facilities or checking facilities. And that's almost impossible to defend, especially when you've got lives that have been lost because of that. So part of the discussion we're going to have is how far back in the supply chain will the FDA inspectors have to go, or will the producers have to go to, and at what cost, because the further you go back, if we're doing it, that means inspectors in a whole chain, if you all do it that means your inspectors that you're paying throughout the whole chain. Can you comment on that or is that just a fair analysis?

Mr. PARKINSON. Well, I think as we listened from the earlier testimony, the resources and manpower to do it is one thing. You need to get, certainly if it's sourced in China, the cooperation from the Chinese locally to go all the way back and do this. As we all understand now, this a very complex supply chain on a biologic. And typically, to enhance safety of products fundamentally you want to focus on inputs and process, hence the inspections. But this happens to be a product where the detection, in terms of when we receive incoming material to our facility, is very critical that we absolutely expose that bulk to the highest level test. And we always have subjected it to more tests than are required by the USP, titer specification, and so on, because it was biologic, because it's from China and because the supply chain is so complex. So it is a daunting undertaking.

Mr. SHIMKUS. Well, let me just—and my questions here by just reiterating the fact that the committee as a whole, the whole committee, is pretty intent on moving something. And I think most of us agree, we as public policy makers with the FDA, we have to break down stovepipes, we've got to get IT and we're going to have to fund it somehow. It would be helpful for us that industry would be partners in this process, and understanding that we're all going have to give a little bit.

So I would encourage you all and folks in the associations at which you may be members of to work with us and the majority here to move something positively that's going to give a better assurance. Because we just feel too many cases right now, not just in the drug issue, but in kids' toys, and in food products, that the public is expecting us to do something. So I appreciate it. Thank you.

Mr. STUPAK. A couple more questions of me. Mr. Parkinson, you sort of indicated that you policed yourself, you didn't see these problems that the FDA found. I'm really baffled by that. How is it you can have just two divergent findings on the same plant? You have your audit that says everything is fine in the fall of ’07 and then they go there in February and they’re just worlds apart. Did anything physically happen in the plant in 5 months?

Mr. PARKINSON. Well, I don’t know. I can only speculate. And what I would say would be repetitive to what I said earlier. Different points in time. It was a snapshot. Ours was what’s referred to as a routine inspection, as opposed to the Agency went in for cause subsequent to the events that transpired. That leads to a very different kind of inspection. Beyond that I can’t really speculate.

Mr. STUPAK. So when the FDA says that at the Changzhou SPL’s processing steps provided no assurance that they were capable of removing impurities, why wasn’t that found 5 months earlier? I mean, removing impurities from a product. It’s the same process to remove it, right, impurities?

Mr. PARKINSON. Well, and there’s impurities that are also removed in terms of when material comes into our facilities as well. I mean, this is a biologic. And at a certain low level there are impurities beyond this one that was introduced.

Mr. STUPAK. But they weren’t getting removed out of your plant, right, in Changzhou?

Mr. PARKINSON. I would defer to Dr. Wang in that regard because I don’t have the technical expertise frankly to respond to that.

Mr. STUPAK. OK. Well, let me ask Dr. Strunce and Dr. Wang this. Either of you, Mr. Strunce, or you Dr. Wang, told our investigators that SPL’s Changzhou plant was essentially the same facility and operation as your Wisconsin facility. Do any of you remember saying that to our investigators?

Mr. STRUNCE. Yes, that’s generally correct. Yes, sir.

Mr. STUPAK. Did you make that statement then?

Mr. STRUNCE. Yes, sir.

Mr. STUPAK. OK. Let me ask you this then. And the only difference was China is a little smaller scale than your Wisconsin facility, right?

Mr. STRUNCE. China is, yes, smaller scale.

Mr. STUPAK. OK. But yet, when your Wisconsin facility was inspected it did not have the same problems as in China. So if they’re exactly the same plant, in fact China is a little smaller, why didn’t the same problems show up, the same facility, same operation you said?

Mr. STRUNCE. Well, and exactly the same facility doesn’t mean exactly the same pieces of equipment, exactly everything is exactly the same. It means the process is generally the same.

Mr. STUPAK. So the process. So which one has the newer equipment, China or Wisconsin?

Mr. STRUNCE. I’m sorry?

Mr. STUPAK. Which one has the better equipment, China or Wisconsin?

Mr. STRUNCE. We recently upgraded Wisconsin. We’ve put in a new purification area. And so probably in that area, yes, Wisconsin has better facilities.

Mr. STUPAK. But you also do it differently, too, don't you? In China, if you find a batch out of sequence or not right out of specifications, you just reprocess it to see if you get it right the second time where in Wisconsin you don't do that, do you?

Mr. STRUNCE. Well, I believe that the reprocessing was all done in China according to a validated protocol.

Mr. STUPAK. Why would you do it in China and not do it in Wisconsin? Why would you reprocess if it doesn't meet the specs in one plant and not the other?

Mr. STRUNCE. It's allowed by the FDA to reprocess according to a protocol.

Mr. STUPAK. So why do you do it in one plant and not the other? If it's allowable, why wouldn't you do it in both plants?

Mr. STRUNCE. I don't know that we don't do it in Wisconsin.

Mr. STUPAK. OK. So you don't know that. In your Wisconsin facility you have a heparin expert on-site, but in China you don't; according to the FDA report and Dr. Wang's testimony, he's there maybe 15 percent of the time. So why is that?

Mr. STRUNCE. The Changzhou facility has very capable and trained people. As far as a heparin expert we have several in the company. Dr. Wang——

Mr. STUPAK. Well, my point being, see, you reprocess in one, you don't in the other, you have experts at one, you don't at the other. It almost seems like you're treating them differently, and it's the ones where you have the least amount of inspections where you reprocess that have these problems. Now, you say it may be one of your suppliers. So let me ask you this. One of your consolidators, Changzhou Techpool Pharmaceutical, is a partner with Changzhou SPL, right?

Mr. STRUNCE. That is correct.

Mr. STUPAK. And it supplies the majority of your crude to your plant in Changzhou?

Mr. STRUNCE. It has supplied a majority in the past and now it's one of two suppliers.

Mr. STUPAK. So this partner could be responsible for introducing the chondroitin into this process, right?

Mr. STRUNCE. The consolidator could, conceivably, but we do not think that that's the source.

Mr. STUPAK. OK. So if you don't think—did you check to see if it was the source?

Mr. STRUNCE. We asked, yes.

Mr. STUPAK. Do you really think if you just simply ask they're going to tell you? Weren't you going to check it and inspect it? I mean, remember your reason for going to China was to monitor your suppliers. Is the way you monitor your suppliers simply asking?

Mr. STRUNCE. We asked them, we tested the material that we got from them, and some was contaminated, just as some was contaminated from the other consolidator, just as some has been contaminated all over the world.

Mr. STUPAK. Well, take a look at No. 8 there, Exhibit No. 8 there under Tab 8. This document references all the workshops that supply crude heparin to Changzhou SPL. Which one of the workshops then could be responsible for introducing the contaminant? It's Exhibit No. 8. That's all your suppliers?

Mr. STRUNCE. Yes, sir.

Mr. STUPAK. So if it's not your consolidator, I guess we're back to the workshops. Any of these be responsible for the chondroitin?

Mr. STRUNCE. Any one is possible.

Mr. STUPAK. OK. What are you doing to try to figure out which one of these might have possibly done it, besides asking them a question?

Mr. STRUNCE. Well, we do routine inspections of the workshops.

Mr. STUPAK. Do you do routine inspections of the consolidators?

Mr. STRUNCE. Yes.

Mr. STUPAK. OK. And in your inspections of your workshops or consolidators did you find any chondroitin sulfate?

Mr. STRUNCE. We found—at the time that we inspected them we found no chondroitin sulfate, nor were we looking for it.

Mr. STUPAK. OK. So since this incident occurred have you gone back and checked your suppliers or consolidators and did you look for chondroitin sulfate?

Mr. STRUNCE. We started inspection, but at a certain point in time the Chinese authorities took over a very extensive inspection and do not feel that we should be interfering with the inspection of the Chinese authorities. The Chinese authorities are——

Mr. STUPAK. Well, the Chinese authorities never inspected your plant to produce heparin. So now you're saying because they said don't check the workshops and the consolidators that you're going to back off? I mean you never even checked your plant, right?

Mr. STRUNCE. That's correct, but there's no relationship between the two facts.

Mr. STUPAK. Well, did you have to get Chinese permission to manufacture heparin in their country?

Mr. STRUNCE. We are a chemical company, according to them, because we built the plant for the sole purpose of providing product to the United States. We don't sell product in China.

Mr. STUPAK. OK. So you're considered, then, a chemical company, not a pharmaceutical company?

Mr. STRUNCE. That's correct.

Mr. STUPAK. All right. So did you get permission to operate as a chemical company in China?

Mr. STRUNCE. We operate—we have all the permits that we need to operate in China in doing exactly what we do.

Mr. STUPAK. Did you notify the FDA, then, you were producing your license in China as a chemical company to produce pharmaceuticals here for the United States?

Mr. STRUNCE. We notified the FDA that we were planning to produce product for the United States market and we filed a drug master file with the FDA and registered.

Mr. STUPAK. Right. That you were planning to do it. But did you ever tell the FDA that you were actually doing it, providing?

Mr. STRUNCE. Of course. I mean we have to provide a drug master file.

Mr. STUPAK. OK. A drug master file. Then what happens after a drug master file?

Mr. STRUNCE. Baxter makes—we give Baxter permission to reference our drug master file. Baxter makes a request to use Changzhou SPL as a supplier. And the FDA approved that.

Mr. STUPAK. OK. But you also know, as Mr. Parkinson indicated, before that was approved it should have been inspected, right?

Mr. STRUNCE. I know they have the right to inspect it. We were perfectly available, waiting, expecting an inspection.

Mr. STUPAK. OK. Don't you think—how long have you been in the business, this pharmaceutical business?

Mr. STRUNCE. About 30 years.

Mr. STUPAK. Have your other plants been inspected by the FDA?

Mr. STRUNCE. Yes, sir.

Mr. STUPAK. Didn't you think it was odd that this one was not being inspected by the FDA?

Mr. STRUNCE. We were surprised that it wasn't inspected by the FDA.

Mr. STUPAK. So in your surprise you never picked up the phone and asked the FDA what's the deal going on, are you going to inspect or not inspect, that it was okay to ship a product?

Mr. STRUNCE. Well, we became an approved supplier according to the FDA. So whether they were going to inspect us prior, or the next week, or the next time they had somebody in China, that is not my——

Mr. STUPAK. The next time they have somebody in China to do an inspection, that's about 30 or 40 years we figure.

Mr. STRUNCE. Yes. You did the calculation. I didn't know that. I thought it would be weeks or months. We have been ready and willing to be inspected, no problem.

Mr. STUPAK. Well, how about this? You know, a lot of us indicate, you saw a chart up there earlier today, that we inspect plants in the United States every 2.7 years, in China it's 30-plus years before you get a chance to inspect it. Is that incentive to go develop drugs overseas because you don't have to put up with the FDA hassle and regulations?

Mr. STRUNCE. Quite honestly, we don't consider the FDA a hassle. We have always been very transparent with the FDA about everything we've done. We're inspected, by the way, more often than 2.7 years. We get inspected 18, 12 to 18 months.

Mr. STUPAK. Where?

Mr. STRUNCE. In Waunakee.

Mr. STUPAK. In Wisconsin?

Mr. STRUNCE. Yes.

Mr. STUPAK. Were you surprised that the FDA, like Mr. Parkinson, were you surprised with the FDA's inspection, all the problems they found, starting with impurities all the way down, that even your manufacturing process wasn't suitable for producing heparin, were you surprised at that inspection?

Mr. STRUNCE. I was surprised at the list of the 483, yes.

Mr. STUPAK. What happened between October of 2007 and February of 2008 when they made that inspection, that 5-month period? Anything happen at the plant that would cause that big dropoff?

Mr. STRUNCE. No, there was no big drop-off. The facility didn't change the way that it produced heparin, it didn't change anything. What changed is the environment and the——

Mr. STUPAK. What changed was the chondroitin somehow got into this drug, right?

Mr. STRUNCE. That's correct.

Mr. STUPAK. And it's one of your suppliers and you don't know which one?

Mr. STRUNCE. It's one of many people's suppliers. There are many companies that have been impacted by this, so it's not just our suppliers. It's our suppliers. Somewhere down our supply stream——

Mr. STUPAK. But you're the only company that can't ship product to the United States?

Mr. STRUNCE. We are the only company that—yes, we are the only company that's on an import alert.

Mr. STUPAK. Right. So it has to be from one of your suppliers?

Mr. STRUNCE. I don't know what that means, sir. I know that heparin has been contaminated all over the world, multiple countries, multiple companies, and it's not coming from us.

Mr. STUPAK. Well, if it's not coming from you——

Mr. STRUNCE. Our product was contaminated, but our product is not the only product that was contaminated.

Mr. STUPAK. So do you think you're being treated unfairly by the FDA then if you're the only company that has the import alert if other companies are supplying heparin that's contaminated to other parts of the world?

Mr. STRUNCE. We are a U.S. company, and I accept the regulation of the FDA.

Mr. STUPAK. But don't you think it's unfair if the others aren't being penalized and you are?

Mr. STRUNCE. I think that any heparin, not only coming into the United States but going anywhere to be used as a pharmaceutical product, should be tested very thoroughly.

Mr. STUPAK. OK. I've been stalling for Mr. Burgess to come back. I see he's back. Do you have questions, Mike?

Mr. SHIMKUS. I'm first.

Mr. STUPAK. Mr. Shimkus, go ahead.

Mr. SHIMKUS. But I'll be short. Mr. Strunce, I think you told me earlier that the China plant is much smaller than the Wisconsin plant, the Wisconsin plant produces two products, the China plant produces heparin only, is that correct?

Mr. STRUNCE. Yes. Only heparin products, yes.

Mr. SHIMKUS. So if you're on the import list, is the Chinese plant closed right now, is it producing, is it selling, where is it going?

Mr. STRUNCE. Since we first heard about the contamination, the plant has been shut down. We are not producing. We are not shipping. We won't produce or ship until we resolve the warning.

Mr. SHIMKUS. Great. The other questions that I have, and you all have the best example, because having a working relationship with the Chinese workforce and the Chinese Government. I think one of the things that frustrated us is that during this whole process when the heparin case burst in the news, many of us recall Chinese officials telling the press that the plant was making heparin for export only and was not making heparin for the Chinese people, so China didn't check on the plant and no one else did. So this gets to the—and you all know, you're businessmen, you all know about corporate culture, culture of industry. Is there a cultural issue as far as—that we should be concerned with on the quality of a product and the concern of the health of our citizens who are receiving product from China? That's an attitude toward quality. You may not want to answer that. Mr. Parkinson.

Mr. PARKINSON. Well, there's a lot of aspects of that question with cultural dimensions to it. I can speak to a specific experience of Baxter's operations that we have. Our own manufacturing plants which we run in China, which we have five, we employ roughly 2,000 people. And I can tell you the quality of the products coming out of those facilities are superb. They are all used locally in China. We don't export our manufactured product outside of China. The caliber of the workforce, their commitment to quality. Frankly, their commitment to quality standards and environmental standards in China, which is defined here in the U.S. as a U.S. company, has been great.

Now, your question has broader ramifications as well, cultural dimensions to it, and I'm not sure how to comment beyond what I've shared.

Mr. SHIMKUS. Mr. Strunce. My concern is the whole, it seems like in this facility, if it's just being sold in the United States and that you met all the requirements to be qualified to have a facility there, export only, it's kind of from the Chinese perspective—they weren't in there, let the buyer beware. And as we were dealing with a multitude of issues as far as import aspects from China, this is that whole cultural debate that we may have to address.

Mr. STRUNCE. Well, I think that, first of all, I believe that the quality, the people that we have in China are excellent employees, they're very dedicated, they've taken FDA training when training has been offered both in China and some actually in the States. And I think from an individual standpoint our company has very dedicated employees. But the supply chain is very long. And I think that we have to be vigilant on the supply chain for the pieces that aren't part of our company. And I think that's where we need to be more vigilant, and perhaps that's an area that as you're looking at a more general picture that might be important also to you.

Mr. SHIMKUS. I think we need to be more vigilant, too. So it's not—as I think we've seen with our FDA.

Mr. Chairman, that's all the time that I need for questions, so I yield back.

Mr. STUPAK. Thank you. If I may, just a quick question or two. Mr. Parkinson, if we can go back to Exhibit 30, page 3. In your inspection there you're saying that there were differences in inspections and difference in degree between yours and the FDA. And on page 3 it says, "the audit scope for manufacturing as well as other potential future projects." What future projects were you going to put in this plant here in Changzhou?

Mr. PARKINSON. We have no specific plans, Mr. Chairman.

Mr. STUPAK. Why would it be in there then?

Mr. PARKINSON. I'm not sure I can answer that question. I don't know. We have no specific plans for future projects in this facility.

Mr. STUPAK. OK. The next page in the background says that the Changzhou SPL employs a system of quality assurance that complies with the highest level of general manufacturing GMP requirements. The highest level. Other than someone adding chondroitin to the heparin, and no one found that at this plant, those highest levels of manufacturing requirements that you say is in there really doesn't meet what the FDA would call the highest level of good manufacturing requirements, does it?

Mr. PARKINSON. Certainly not based on the results of the recent inspection.

Mr. STUPAK. OK. Let me ask you, both Mr. Parkinson and Mr. Strunce, there's been some talk about the economics here of using the heparin and using chondroitin, a difference in cost, and I think Mr. Burgess asked some of those questions of an earlier panel. There was the blue ear disease that went through and wiped out a lot of the swine population in China, right?

Mr. PARKINSON. That's my understanding, yes.

Mr. STRUNCE. That's correct.

Mr. STUPAK. Did you ever discuss using the substitute for heparin, then, other than pigs' intestines in your manufacturing process?

Mr. STRUNCE. Absolutely not.

Mr. STUPAK. OK. Mr. Parkinson?

Mr. PARKINSON. No.

Mr. STUPAK. OK. Dr. Wang, in this report, and again in this exhibit, Exhibit 32, this is the Chinese or translation was Chinese, I take it, the patent invention application, and one of the inventors is a Fang Sheng Wang. Any relation to you? That would be like Smith in the United States?

Dr. WANG. There are probably 100 million Wangs in China.

Mr. STUPAK. Right. But no relation?

Dr. WANG. No connection.

Mr. STUPAK. Were you aware of the application to use chondroitin, over-sulfated chondroitin in China, the application?

Dr. WANG. No. I only stumbled on this patent application about a month ago.

Mr. STUPAK. Were you aware of it being in the United States from way back when when they used it?

Dr. WANG. No.

Mr. STUPAK. In fact, in the United States, and the next tab actually mentioned about using chondroitin and heparin. That would be the next tab, it would be 33, on the second page, sort of mentioned it. Were you aware of that one? We're on the top of the second page: The invention contained sulfated and chondroitin sulfate type. Do you see where that is? We're on the top of the page—or any prescription. It goes on further and talks about heparin. Were you aware of this patent?

Dr. WANG. No.

Mr. STUPAK. OK. Seeing no further members to ask questions, we'll excuse this panel and move on to our last panel. Thank you, gentlemen.

I would like to have our fourth panel of witnesses come forward. It's Dr. Clive Meanwell, who is the Chair and CEO of The Medicines Company. Welcome, Doctor. It's the policy of the subcommittee to take all testimony under oath. Please be advised that witnesses have the right under the rules of the House to be advised by counsel. Do you wish to be advised by counsel?

Dr. MEANWELL. No.

Mr. STUPAK. OK. Then I'm going to ask you to rise, raise your right hand and take the oath.

[Witness sworn.]

Thank you, Doctor. You're under oath. I will ask for an opening statement if you would. It will be 5 minutes. Then we can put a longer statement for inclusion in the record if you so desire. Doctor.

STATEMENT OF CLIVE MEANWELL, M.D., CHAIRMAN AND CHIEF EXECUTIVE OFFICER, THE MEDICINES COMPANY

Dr. MEANWELL. Thank you very much. Good afternoon. My name is Clive Meanwell. I'm a physician, medical researcher, and the Chairman and CEO of The Medicines Company in New Jersey. In the interest of full disclosure let me say that we market bivalirudin, an intravenous blood thinner that is an alternative to heparin in heart angioplasty and is undergoing FDA review for other uses. In addition, legislation is being considered that could affect the patent life of our product. But I'm not here to talk about that today. I am here because I'm experienced in global research, development regulation, and commercialization of blood thinners, including heparin, and I hope that I can help you to protect patients in need.

Throughout history, medical disasters have spurred legislative, regulatory, and scientific innovation. Dangerous adulteration and misbranding of foods and drugs was a common practice worldwide in the 19th century, when for example American soldiers were given adulterated quinine products. A horse named Jim was used to incubate an antitoxin to diphtheria in the early 1900s. After the deaths of 13 children who received the antitoxin, authorities discovered that Jim had developed tetanus and contaminated the product. These and other scandals drove early regulatory innovation that led Congress to enact the Biologics Control Act of 1902 and the Pure Food and Drug Act of 1906.

Another therapeutic disaster in the 1930s, when a chemist formulated sulfur with a substance we now call antifreeze, killing at least 100 people, including many children, led to the Food, Drug and Cosmetic Act of 1938.

And yet another therapeutic disaster involving thalidomide compelled passage of amendments to the Food and Drug law in 1962.

heparin was discovered over 100 years ago and by 1935 researchers recognized its therapeutic value as a rapid and powerful injectable blood thinner. Most heparin is now manufactured from pig intestines using methods developed in the 1950s. Today, heparin is, as we've heard, ubiquitous in U.S. hospitals and more than 10 million patients are given the product each year. We've also heard that it's estimated half the world's crude heparin supply now originates in China, where the supply chain may include unregulated participants. Some experts estimate that 70 percent of China's crude heparin comes from small producers. Production facilities may be quite rudimentary and small producers may not keep records of the source of pig intestines or other information.

In the warning letter described today, the FDA effectively shut down imports from one Chinese manufacturing facility because of deficiencies concerning sources, methods, equipment, and records.

The average price of heparin in the U.S. is $1.75 per unit. While low cost medications can represent an enormous benefit to patients, razor thin margins can also carry risk if producers are unable to invest in global quality systems.

Apart from these manufacturing problems, even properly produced heparin has well-known limitations as a drug, particularly in high risk patients. These include variable levels that affect serious and sometimes fatal bleeding and occasionally life-threatening immune reactions.

Let me provide a perspective on what might be done going forward. First, when the drugs are produced in or outside the U.S. by themselves or by third party contractors, manufacturers must develop global quality systems. We cannot assume that FDA or other regulatory agencies will take care of quality control.

Second, the FDA needs to allocate inspection resources matched to the global business of pharmaceutical manufacturing. Eighty to 90 percent of active ingredients are now made outside the U.S. That means far more inspections should be made abroad and the FDA must recruit, train, and support inspection staff accordingly.

Third, there needs to be much better coordination between regulatory agencies in countries with high quality standards.

Fourth, we need better science and testing processes. In last week's publication of two articles on contaminated heparin, FDA produced excellent interdisciplinary science very quickly when the need arose. Congress should support advancement of key regulatory science capabilities.

And finally, as highlighted by this heparin crisis, we need not only to assure safety in the production of existing drugs, but also encourage new product innovation. Heparin has been a workhorse drug since the 1930s, but with limitations. Biotechnology has recently produced next generation alternatives to heparin, and further research is needed to prove greater safety and effectiveness, particularly in high risk patients such as those undergoing dialysis, heart surgery and stroke prevention or treatment. In my view, Congress should continue to support measures that encourage such innovation.

Mr. Chairman, I would be happy to take questions.

[The prepared statement of Dr. Meanwell follows:]

Testimony of Clive Meanwell

Before the House Energy and Commerce

Subcommittee on Oversight and Investigations

April 29, 2008

Good morning Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee. My name is Clive Meanwell and I am a physician, medical researcher and the Chairman and Chief Executive Officer of The Medicines Company, a small, New Jersey maker of acute care medicines used in hospitals. We have one product currently approved for use – bivalirudin, which we sell under the name Angiomax – and we have other products in our pipeline. Bivalirudin is an intravenous blood thinner and, in its approved uses, a substitute for heparin. In 2005, I authored a chapter titled Antithrombotic Drugs and the Pharmaceutical Industry dealing with the research, development, regulation and commercialization of blood thinners, including heparin and novel alternatives, worldwide.[1] Prior to my current role I was head of worldwide regulatory affairs at a major pharmaceutical company which marketed heparin.

I appreciate the invitation to appear before you today. Based on many years of experience in helping to develop and commercialize blood thinners and other drugs for U.S. and European pharmaceutical companies, and my experience of working within both U.S. and European regulatory systems, I hope to offer some perspective on the issues with which the Congress, the FDA, health care professionals, patients, and the pharmaceutical industry are now grappling. Let me also say, in the interest of full disclosure, that my company has pending applications with the FDA to extend the use of bivalirudin to patients with pre-heart attacks and patients with heparin allergy undergoing heart surgery. Further, we have been requested by the FDA to study the drug in children and that study is ongoing. Finally, we also have interest in pending legislation that is relevant to our capacity to extend bivalrudin to other treatments where heparin is currently used, including open heart surgery and stroke, but I am not here today to address that legislation.

---

[1] Meanwell CA. Antithrombotic Drugs and the Pharmaceutical Industry. In: Becker RC and Harrington RA (eds). Clinical, Interventional and Investigational Thrombocardiology. Taylor & Francis, Boca Raton 2005. pp 696

Historical Perspective – Medical Crises Have Led to Constructive Change

Throughout history, medical disasters and scandals have spurred many forms of innovation. The innovation has been legislative – new laws to regulate medical products. It has been regulatory – new FDA regulations to control problems like adulteration or misbranding. And it has been scientific – as inventors, innovators and regulatory scientists in the United States have time and again come up with new solutions to improve the safety, health and welfare of patients in need.

The current heparin crisis is another tragic chapter in this story, and highlights the critical importance of such innovation – now on a global basis.

Dangerous adulteration and misbranding of foods and drugs was a common practice worldwide in the 19th century. Quinine-containing cinchona bark powder sold to the United States army was made more profitable, but much less effective and safe, by cutting it with just about anything from oak bark to mahogany dust.[2] Formation of the Division of Chemistry in 1862, pioneering work by its Chief Chemist from 1883, Harvey Washington Wiley, and passage of the Food and Drugs Act by Congress in 1906, established federal ways and means to protect Americans from the most egregious adulteration.[3] An even better solution came from the American Nobel Prize winning chemist, Robert Burns Woodward in 1944 – an important time for American inventiveness – when he synthesized pure quinine salts and paved the way for industrial production.[4,5]

---

[2] Cyclopaedia of Six Thousand Practical Receipts, and Collateral Information: Published 1854. D Appleton & Co.

A horse named Jim was used to incubate an antitoxin for diphtheria in the early 1900s. After the deaths of 13 children who received the antitoxin, authorities discovered that Jim had developed tetanus, and contaminated the antitoxin. Congress passed the Biologic Control Act of 1902, giving the government regulatory power over antitoxin and vaccine development. Incubation in eggs – and more recently recombinant DNA techniques – have since provided high-tech solutions to many of the problems of vaccine production, purity and safety.

It took another therapeutic disaster to propel new legislation through Congress in 1938. The year before, in an effort to make sulfa drugs more widely available in the United States, a chemist mixed up sulfa with a substance called diethylene glycol (which we now use as antifreeze). There was no legal requirement to study the product in humans or even in animals before making it widely available, no such studies were done, and the result was a therapeutic disaster that caused at least one hundred deaths, many in children. Legislative and regulatory innovation followed immediately. FDA conducted the first large-scale recall of a product, in some cases using its staff to go from pharmacy to pharmacy to pull the product off the shelves. Congress passed and Franklin D. Roosevelt signed the Food, Drug, and Cosmetic Act of 1938, requiring for the first time that FDA be given the opportunity to review New Drug Applications demonstrating the safety of a product before it could be marketed.

---

[3] History of the FDA. http://www.fda.gov/oc/history/historyoffda/default.htm. *Accessed* 27th April 2008

[4] James, Laylin K., ed. (1993). *Nobel Laureates in Chemistry 1901–1992.* Washington, DC: American Chemical Society; Chemical Heritage Foundation.

[5] In 1970, Milan R. Uskokovic′ and coworkers at Hoffmann-La Roche in Nutley, N.J., disclosed the first total synthesis of quinine, although stereocontrol was still incomplete. Chemical and Engineering News: http://pubs.acs.org/cen/coverstory/83/8325/8325quinine.html *accessed* April 23, 2008.

Yet another therapeutic disaster compelled passage of amendments to the food and drug law in 1962. In the early 1960s, thalidomide, a sedative used by pregnant women, caused thousands of grossly deformed newborns in Europe. The disaster was averted in the United States because the New Drug Application for the product was still under review by FDA at the time the European problem became well-known. But Congress nevertheless reacted to this international crisis by tightening the regulation of drugs in the United States in many important ways, including requiring proof of efficacy as well as safety prior to marketing a drug and giving FDA authority over manufacturing processes and the clinical investigations of drugs. In addition, Congress mandated a review of a long list of drugs that had been introduced between 1938 and 1962, a list that included heparin.

In addition to triggering regulatory innovation at FDA, the 1962 amendments set off a wave of scientific innovation. FDA's issuance of regulations explicating the efficacy provisions of the new law was accompanied by intensive work by clinicians and scientists, both inside and outside of FDA, to design and carry out new and better studies of drugs. FDA's issuance of regulations governing good manufacturing practices was accompanied by intensive work by chemists and process engineers, both inside and outside of FDA, to develop methods to assure that manufacturing processes reliably produced drugs that were as safe and effective as they were intended to be.

But now we are reminded, because of the heparin situation and others like it, that the need for innovation – legislative, regulatory, and scientific – is constant. No matter how good the legislation, or the regulation, or the science, old problems recur, and new ones occur. And we find this particularly true in the last 25 years as the nature of drug development, commercialization and manufacturing has gone truly global. A large proportion of this manufacturing has moved to India and China.

Heparin – Current Challenges

Heparin is practically ubiquitous in U.S. hospitals, with more than 10 million patients receiving the product each year. The main FDA approved uses for heparins are to prevent or treat blood clots in peripheral veins and arteries; in the lungs; during arterial and cardiac surgery; and during heart rhythm disturbances when there is a risk of stroke. Heparins may also be given to diagnose or treat serious blood clotting disorders, or to thin the blood during blood transfusions, kidney dialysis and while patients are on heart-lung machines. A staggering 79 million dosage units of standard heparin, 55 million units of low molecular weight heparin and 47 million units of heparin flush (used to keep injection lines open) are used each year in U.S. hospitals.[6]

Heparin was discovered in the late 19th century, and by 1935 researchers recognized its therapeutic value as a rapid and powerful blood thinner.[7] In the early days, heparin was extracted from dog liver, beef liver, or on an industrial scale, from beef lungs. But in the 1980s, the emergence of "mad cow disease" led manufacturers to switch to pigs.[8] Today, most heparin is manufactured from pig intestines. Current manufacturing and analytical methods are based on those developed in the 1950s in which the tissue is coagulated in boiling water and subjected to prolonged and repeated digestion using pancreatic enzymes. The concentrated digest is separated with ethanol then purified with aluminium silicate and further ethanol. This gives a crude mixture of sulphur-containing sugar chains which can be further separated into crude heparin and other residual complex sugars.[9]

---

[6] Third party hospital audit data on file: units may be single or multiple use vials, pre-filled syringes or other dosage forms.

[7] Mueller RL and Scheidt S. Circulation 1994; 89:432-449

It is estimated that at least half the world's crude heparin supply is produced in China, and the supply chain there often includes a variety of participants, many of them unregulated. Some heparin processing facilities in China are modern and well-equipped, but, according to some experts, as much as 70 percent of China's crude heparin comes from small producers. Extraction and production facilities can be quite rudimentary, as has been recently reported. Some are family-operated, unregistered workshops that collect and process pig intestines. Press reports recently described some of these workshops as dilapidated and unheated with drainage channels and large puddles on the floor, and families living in a back room of the same building. These small producers may not keep records of the source of pig intestines or other critical in-process information. After they've produced the crude material, they often sell it to middlemen. This creates a supply chain with many players and little, if any, documentation.

---

[8] Meanwell CA. Antithrombotic drugs and the pharmaceutical industry. In: Becker RC and Harrington RA (eds). Clinical, Interventional and Investigational Thrombocardiology. Taylor & Francis, Boca Raton 2005. pp 696

[9] Jaques LB and Bell HJ. Determination of Heparin. Methods of Biochemical Analysis. Volume 7. Interscience. 1959

Earlier, I described the remarkable volume of heparin use in the United States. But the average unit price – usually enough to treat a patient for one or more days - is only $1.75. Thus, an essential hospital product used in very sick people is priced well below a box of Bandaids. While low cost medications can represent an enormous benefit to patients, we need to be mindful that razor thin margins can also carry risk if producers are unable to invest in manufacturing improvements and quality control throughout the global supply chain.

In a Warning Letter it sent to one Chinese manufacturer, FDA concluded that there were significant deviations from U.S. Current Good Manufacturing Practice, citing four main concerns: that (1) the plant had not established impurity limits for heparin or shown that it could consistently remove impurities; (2) the plant had failed to establish adequate systems to evaluate the suppliers of heparin materials or the crude materials themselves; (3) the plant's testing methods could not reliably detect and quantify the presence of proteins in the API; and (4) the equipment used to manufacture heparin is unsuitable for its intended use, with "unidentified material" stuck to the inside surfaces of tanks, scratched surfaces of the tanks and unqualified cleaning methods for tanks.[10]

Apart from the specific manufacturing problems that the FDA is investigating, heparin has therapeutic limitations even when manufactured correctly. As a natural animal extract, heparin comprises a heterogeneous mix of complex sugar chains of different lengths and inter-linkages, which can vary from manufacturing batch-to-batch. Although heparin has come to be regarded as the workhorse blood thinner in hospitals, this lack of chemical consistency imposes well known limitations on its performance as a drug.[11]

---

[10] US FDA Warning Letter April 21 2008 to Changzhou SPL Company Ltd.

Solutions as We Look Forward

With that as background, I would like to provide a perspective on how innovation can help to prevent problems, and mitigate them when they occur.

First, manufacturers need to develop innovative global business processes and take responsibility for methods, components and final product quality, whether drugs are produced in or outside the United States, by themselves or by third party contractors. There is no reason to believe that FDA should shoulder these complex responsibilities – though FDA obviously needs to create the regulatory framework and hold the industry to world-class standards. Manufacturers cannot assume, nor should they be allowed to assume, that FDA will take care of the quality control. As Professor Alastair Wood put it last week: "Although the desire to obtain the lowest cost supplies is understandable, this shift comes with additional responsibilities for manufacturers who must ensure the quality, chain of custody, and integrity of their supply chain, especially by supervising the manufacturing process in countries whose regulatory environments are more lax than ours."[12] Nobody wants to cut costs by cutting corners.

Second, FDA and other regulatory authorities need to conduct inspections and allocate resources in a manner that is matched to the globalization of medical manufacturing. According to an article in last week's *New England Journal of Medicine*, the proportion of active pharmaceutical ingredients supplied by U.S. and European manufacturers has declined from 90% to less than 20% in the last two decades.[13] That means far more inspections of the plants should be taking place outside the United States, and that FDA must align its inspectional staff accordingly.

---

[11] Hirsh J and Raschke R. Heparin and low molecular weight heparin: The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:188S-203S

[12] Wood AJJ. New England Journal of Medicine 2008;358:1774

Third, and following on the same point, there needs to be much better co-ordination between regulatory bodies. In testimony last week, FDA Commissioner von Eschenbach suggested the need to coordinate inspections of medical products plants with the regulatory agencies of other countries, including the European Community. With the need for more inspections outside the U.S. ever more evident, we need to find ways to work with the European Community and others whose regulatory authority and inspections are as rigorous as ours to avoid duplicative inspections of plants in other countries, thus multiplying the number of inspections we can do. Working across borders is challenging – even for scientists. So the agencies involved, including the FDA, will need to continue to develop transnational attitudes and skill sets that have generally proved challenging in our 21st century world.

Fourth, we need to apply better science to manufacturing and testing processes. Scientific alarm bells were set off by the Report of the FDA Subcommittee on Science and Technology last year which concluded that science at the FDA is in a precarious situation, not positioned to meet current or emerging regulatory responsibilities.[14] There is no way to test every drug for all possible contaminants and adulterants – unless you have some idea of what you are looking for, you cannot test for it. But with its recent publication of two articles on contaminated heparin associated with adverse clinical events, FDA has shown that it is capable of performing outstanding interdisciplinary science very quickly when the need arises.[15,16] What other kinds of interdisciplinary regulatory science can be applied to the analysis of adverse events, chemical structure of drugs, and other indicia of possible difficulties? Last year also, Congress established the Reagan-Udall Foundation to identify and address unmet scientific needs in the development, manufacture and evaluation of the safety and effectiveness of FDA-regulated products, including post-market evaluation. The foundation will establish scientific projects and programs to address those needs and help accomplish the scientific work FDA needs to support its regulatory mission. If there is more to do to nurture and advance these key regulatory science capabilities, it should be done.

---

[13] Schweitzer SO. New England Journal of Medicine 2008; 358:1773-1777

[14] FDA science and mission at risk. Report of the Subcommittee on Science and Technology. Rockville MD. Food and Drug Administration, November 2007

Fifth, and as illustrated very well by heparin, we need to not only seek to assure safety in the production of existing drugs that may be useful but limited, but also to encourage innovation in new manufacturing processes and new products. Heparin, as noted, has served us well since the 1930s, but it has limitations. Scientific innovation has produced a variety of next generation substitutes for heparin over the last years. These include the important advance of low molecular weight heparins as "standard heparin," whose innovative manufacturing methods have produced a much more homogeneous product, although they are made from pigs. Other recent innovations include injectable blood thinning products not derived from animal sources. The short synthetic form of a heparin sugar chain, fondaparinux, has been introduced into the world market with some

---

[15] Takashi KK et al. New England Journal of Medicine 2008; www.nejm.org April 23, 2008 (doi: 10.1056/NEJMoa0803200)

[16] Guerrini M et al. Nature Biotechnology 2008; published online 23 April 2008 (doi:10.1038nbt1407)

success among patients with leg vein thrombosis.[17] In addition, biotechnology has produced the so-called direct thrombin inhibitors which include lepirudin[18] and argatroban[19] to treat specific forms of immune reactions induced by heparin, and bivalirudin,[20] which is now used by preference over heparin in almost half of the heart angioplasty procedures performed in the United States each year. There is a real expectation that American innovation can take us way beyond heparin.

In summary, Mr. Chairman, history tells us that innovation can move us beyond medical tragedy. With the current challenges of heparin in mind, innovation can include legislative, regulatory, manufacturing and product improvements that will substantially enhance the safety and welfare of patients – and reaffirm U.S. leadership in life-sciences worldwide.

---

[17] Arixtra®, GlaxoSmithKline

[18] Refludan, SanofiAventis

[19] GlaxoSmithKline

[20] Angiomax®, The Medicines Company

Mr. STUPAK. Thank you. And thank you for your testimony. Heparin has been used since the 1930s, I think was your earlier testimony, is that correct?

Dr. MEANWELL. Yes, sir.

Mr. STUPAK. What—besides heparin, what else do they use right now for blood thinners?

Dr. MEANWELL. There are a number of new drugs, one from France called Arixtra, is an ultra short, five-sugar sequence.

Mr. STUPAK. Has that been approved by the FDA already?

Dr. MEANWELL. Yes, sir. And that's on the market for the prevention and treatment of leg vein thrombosis, particularly associated with surgery. Three other drugs are approved. One of them is our drug, I'll come back to that in a second. There is a drug called Argatroban, which is from Glaxo, which is a product from a biotechnology company in Texas, which is to treat patients who are allergic to heparin who can no longer receive it. There's a second of those drugs called Lepirudin, which is from a German company which is also on the U.S. Market. But both of the ones I've just described are used in very small numbers of patients so far.

The third drug is the product we've developed and are marketing. We can only market it today for patients undergoing acute coronary angioplasty. And we are doing other studies under the supervision of the FDA to try to expand its uses.

All of the drugs I've mentioned have a completely different mechanism of action to heparin, have a completely different mode of manufacturing and each of them is synthetic.

Mr. STUPAK. Is the cost per dose about the same with these four or is heparin a much more inexpensive alternative?

Dr. MEANWELL. Heparin is definitely the bottom of the market in terms of price, and these other drugs are considerably more expensive. Each of them has undergone testing, which includes health economic testing. In our own case we determine that we can save the hospital about $500 each time it's used even after taking into account the additional price.

Mr. STUPAK. So it's the least expensive, but it's the most widely used because it has more applications than the other blood thinners, heparin does?

Dr. MEANWELL. Sir, I think that heparin is an outstanding drug in low-risk situations because it does a pretty good job. But when patients get in a high-risk situation, heparin has a tendency to give up on you just when you need it most, and there I think it sort of runs out of steam as an effective and safe agent.

Mr. STUPAK. Let me ask you this. In the witness book there, that big black book right there, would you take a look at 34. And I want to go to about page 7.

Dr. MEANWELL. In section 4, sir?

Mr. STUPAK. Thirty-four, page 7. There's a—Kyle, if you can try to bring that up. We do not have a good copy of this chart, and we just scanned it in. Let's see if it will work. Because I asked the last panel a question about this blue ear disease that hit the pigs or pigs in China which we lost quite a bit of their—you lost your counsel? OK. You can't see it either. Here is what I was trying to get at. When we look at this chart, and maybe you can see it, there's a yellow line that goes through.

Dr. MEANWELL. It's not clear, but I do see it, yes.

Mr. STUPAK. And the average cost of crude heparin, as you see in about 1990 went way down using the yellow line, and it was pretty well flat and went down. And then in about 2006 it shot way up and actually exceeded what it cost here in the United States to make heparin in about 2007. And that's when that blue ear disease broke out in 2006 suddenly, then the cost of heparin from pigs intestines just skyrocketed in China. And then that's where some of us suspect the adulteration, if you will, occurred with the chondroitin. And I wish that map would have showed it, but it's one of those things. In your research and your development here of your alternative, if you will, to heparin, had chondroitin been looked at as—sulfate chondroitin—as a possible substitute instead of the sugar molecules from the pig intestines?

Dr. MEANWELL. Chondroitin itself, three major products of boiling up pig intestines are heparin, dermatan sulfate, and chondroitin sulfate. Dermatan sulfate is a fairly common impurity that is tested for, has a very minor anticoagulant effect, unreliable, and certainly wouldn't be a good therapeutic. Chondroitin sulfate is even worse. Although it does have molecular structure that might suggest it would be a blood thinner, in reality when you put it in place it wouldn't be. Particularly when Dr. Woodcock mentioned the special structure of this particular chondroitin sulfate, heavy sulfated, doesn't appear in nature, the nearest thing that researchers have found in the animal kingdom is chondroitin sulfate from the cartilage of the squid.

This is not an anticoagulant. This drug has been used, or a similar structure drug has been used, as an oral agent in Europe for joint pain. It was put on the European market and actually taken off the European market even as an oral—excuse me, subcutaneous drug—because it provided anaphylactic reaction.

So chondroitin sulfate, although people may patent it as such, is not even close to something that we in the United States or in Western science would call a drug for blood thinning.

Mr. STUPAK. So is it fair to say—and we don't know other than some upstream suppliers, according to our last panel—the person who, or however it got in there, thought it would be appropriate? Is it possible to make that assumption? He thought it would be appropriate, but in reality it does not; there's a patent in China, there's a patent in the United States to use a chondroitin in heparin, and it was just an educated guess that didn't look at the safety ramifications? Is that fair to say?

Dr. MEANWELL. Sir, I think it is fair to say. I think someone with good chemistry, lousy medicine, and no ethics could do that.

Mr. STUPAK. OK. Because our information technology is better than the FDA's, Kyle was actually able to color that yellow line. So you can see how at one time the heparin from the pigs is—the red line from China was higher than—the other line there is from the U.S. domestically produced.

One time it was higher, then it dropped way down in the 90s there, and then right about the time we had that blue ear outbreak, you can see how the red line just shot above what's domestically being produced.

So thanks, Kyle, for doing that so we could see it.

With that, I will turn to Mr. Shimkus for questions please.

Mr. SHIMKUS. Thanks, Mr. Chairman. I just want to follow up on that same slide.

Mr. Meanwell, should that price spike in the pig shortages, should that have raised red flags to the heparin producer?

Dr. MEANWELL. I was asked that question a couple of days ago, and I'm not an expert in supply purchasing. But I called some people I know in the industry who are, and I asked them that question. I said, if this happened to your supply chain, what would you do?

I think what we all know is that most—this local pharmaceutical supply chain that has been discussed today is mostly governed by contracts. Those contracts set up provisions for price, quality, delivery times, and specifications. And typically, if you go outside of the specs of one of those contracts—say, by 5-plus or 6-plus percent—in other words, more than inflation—first, it would raise a commercial flag. Is this really the best supplier I can get?

I pushed a couple of people on it, experts, and they said, Well, if it was 100 percent, I need to know why; I've got to know why.

So if you then find that blue ear disease is behind it, that's a reasonable explanation. But then I think one has to ask the question, is this going to be a temptation if I'm not completely sure of my drug supply, and I think common sense would suggest it would be a temptation.

Mr. SHIMKUS. So it should have been a red flag?

Dr. MEANWELL. I believe so, yes.

Mr. SHIMKUS. And following up—and you said, to a lot of the other questions and the debate, does—China still is—some people are trying to define—it's still developing, but there's parts of it that are very developed.

Does relying on China for commodity products of this magnitude with the inspection regimes, or the inspection regimes that we don't have, does China present particular challenges on this front?

Dr. MEANWELL. I think we know that Chinese science can be outstanding. We know that Chinese production methods can be outstanding. But I think we also know that their pharmaceutical industry is emerging as a global player, and certainly I think it behooves us to be quite cautious in sourcing materials from, frankly, any developing nation.

So I don't think there's anything special about the culture of China that makes them—which might have been implied earlier that makes them less careful. I think Chinese people are extremely careful about this kind of thing. But there may be a need for them to develop skills and systems.

Mr. SHIMKUS. The product that you are referring to, that you're involved with, is it licensed in Europe?

Dr. MEANWELL. Yes, it is, sir.

Mr. SHIMKUS. But not here yet?

Dr. MEANWELL. It is approved—as I mentioned in my opening remarks, it is approved for a narrow use, which is coronary angioplasty. We are pursuing other uses for it with the FDA's support.

Mr. SHIMKUS. I didn't have angioplasty. We're kind of sharing time and sharing questions. So that's a good sign.

Are there possibilities—we were talking about just the cost-benefit analysis, and we know heparin is a workhorse drug; it has been around for a long time. I think you highlighted the fact that it shouldn't be used in some cases when the patient has a lot of other challenging aspects. But there's this whole cost. We know the high cost of new drugs that come to market versus drugs that have been around for a long time, and there's—there is that challenge.

Are there possibilities that synthetics for heparin and other animal-source drugs can be developed and produced that would reduce our reliance on the supply from China?

Dr. MEANWELL. Well, most of the drugs I'm talking about are synthesized in Europe and/or the United States, or both. So, by fact, that would be true.

However, I have to point out that the volume, the sheer volume of heparin used in the United States hospitals is enormous. Seventy-nine million units of heparin were—if we look at a moving annual total, as of March 2008, so we'd have to replace 79 million units, and that's a whole lot of heparin.

As I said, I think heparin is a very good drug in the right places at the right time.

Mr. SHIMKUS. Would you consider synthetics a more—I think you highlight that might be difficult because of the supply. But would synthetics be a more secure pipeline, that we wouldn't have the long tail of product line?

Dr. MEANWELL. I believe, earlier, that Dr. Woodcock or Dr. Autor mentioned that the newer drugs coming to the market tend to have a tighter quality chip, if you like.

Quality control systems are sort of built in during drug development these days. Obviously, when heparin came to the market in the 1930s, such things weren't yet understood so well. So I think we've never really gone back and engineered all that quality in them.

So I think new products coming along tend to be better controlled in general than older products, for those reasons.

Mr. SHIMKUS. And maybe some of the control would be for the proprietary information of producing the synthetic drugs, too, versus being more—not as controlled and then losing the ability to other people who may just reproduce it based upon patent infringement or something.

Dr. MEANWELL. I think that's true. But I think the principal reason to pursue the quality, which was also mentioned earlier, is patients and reputation.

Mr. SHIMKUS. Mr. Chairman, that's all the time I need.

Mr. STUPAK. Thanks, Mr. Shimkus.

Mr. Burgess for questions.

Mr. BURGESS. Thank you, Mr. Chairman. And Dr. Meanwell, thank you for sticking it out through a very long day here, our committee work.

I really do have to tell you, I appreciated so much your coverage of the history of so many aspects of this debate that we're in today, because I think it is important to put it into historical perspective.

A couple of things that were in your testimony that were also intriguing:

Number one, you have the comment that the Food and Drug Administration is capable of performing outstanding and interdisciplinary science very quickly when the need arises. And I think that observation was made by one of the other panels here today.

But we at this end where we're referenced by a New England Journal article from this morning, where we're quick to kick the FDA, we also need to recognize that the resource is one that does—that does provide a valuable service, and a valuable service to not just physicians in this country, but to patients in this country as well.

I appreciate so much your bringing that up in your testimony because again, it's something that I think that gets lost in translation here all too often.

You also talk a little bit about some of the work we did in June with the formation of the Reagan-Udall Foundation, which I also thought was a good idea. Now, my understanding is—during our last appropriations process, and that was a USDA appropriation—that the funding for the Reagan-Udall Center was blocked. Is that correct?

Dr. MEANWELL. I don't know, sir.

Mr. BURGESS. The think the answer is, yes it was. I know that because I read it in a Wall Street Journal editorial, and they were quite concerned that one of the few things that Congress had done this year was—on an authorizations standpoint was not—the money was not forthcoming for an appropriation. And it was unfortunate, but the reason given for blocking the appropriation was that it would somehow be one more gift to give to the pharmaceutical industry in this country when they really didn't need anything else from Congress.

Another statement that you have in here, "Manufacturers cannot assume nor should they be allowed to assume that the Food and Drug Administration will take care of quality control." Again, a point that I think is sometimes missed on this committee. But that's a fairly powerful one. And you follow that up with a quote which I won't quote, but end up, "nobody wants to cut costs by cutting corners."

Does not that go to the statement made by the witnesses from the Food and Drug Administration, when the comment was made, "The best way to ensure integrity of the supply chain was through the manufacturer itself." Is that correct?

Dr. MEANWELL. Well, I don't think there's any single solution, but I have a perspective from being—living abroad, being British, having worked in the European pharmaceutical industry.

When the FDA arrives at your plant, everyone stands to attention. It's the gold standard. They perform outstanding work. They perhaps don't perform enough of it, but when they do it, they do it really well.

But then, in addition to that, I think there are other factors, such as improved regulatory science that is being supported that is also needed.

And then, finally, the industry has to play its role. We are the manufacturers, and therefore, I think we have to take ultimate accountability for the quality of the product. I believe that my colleagues in the industry all agree with that.

Mr. BURGESS. But then we heard testimony from Mr. Nelson on the first panel. I think the statement he made was, “Corporate due diligence cannot be relied upon,” which seems to be counter to that philosophy that you just expressed.

Dr. MEANWELL. Well, I wasn’t clear, in that case.

It’s my view that the company has to do everything it can to assure the quality throughout the process. I think the FDA has to set the bar. The FDA has to set world-class standards. And the industry should say, okay we’ll jump over that bar.

I think it’s a duality required; and then underpinning both of those key factors is the ability to do outstanding regulatory science of the kind you saw in the New England Journal of Medicine last week.

Mr. BURGESS. Let me ask you a question: now you are working on a compound that may replace heparin as a synthetic; is that correct?

Dr. MEANWELL. It’s currently replacing heparin in angioplasty. It is now the leading blood thinner used in those cardiac procedures, and we’re developing it for heart surgery, for stroke prevention and for arterial blood clots.

Mr. BURGESS. So these are approved uses.

Dr. MEANWELL. No, they are not. They are all the ones under development with protocols running.

Mr. BURGESS. In angioplasty, it is an approved use.

Dr. MEANWELL. Yes, sir. Yes, it is.

Mr. BURGESS. What’s the cost per unit dose.

Dr. MEANWELL. Approximately $570 to use the drug in angioplasty.

In the health economic perspective studies completed by Harvard, in association with our large, randomized, phase 3 pretrials, even after paying $570 for the drug, the cost saving in an acute heart attack patient or pre-heart-attack patient was still $800, because it reduces bleeding, because it reduces side effects.

Mr. BURGESS. Now, heparin in that instance would not be—would not be useful, would not be interchangeable with the product that’s under development?

Dr. MEANWELL. It would be interchangeable.

And heparin in that situation is practically free. We’re talking about a handful of dollars’ worth of heparin by comparison. But in order to use heparin safely in a heart disease patient, you have to add on all other kinds of expensive drugs as well to protect the patient.

This was my point earlier, that in the workhorse setting, heparin is excellent. When we really ask it to take care of patients who are extremely sick, undergoing heart surgery, heart procedures, or having heart attacks, it’s not quite up to the job.

Mr. BURGESS. But in a workhorse environment, would there ever be a place where the synthetic product could replace heparin just because of the—because of the sheer volume that you alluded to, that it would be—with the manufacturing process, allow it to keep up with that volume?

And then, on a cost basis, would it ever be competitive with heparin?

Dr. MEANWELL. It's quite difficult to imagine any injectable drug in the current era being sold for a dollar a shot.

Mr. BURGESS. Yes, it sure is, isn't it?

Dr. MEANWELL. It really is. It's extraordinary, actually.

Mr. BURGESS. And as a consequence, of course, the company that's under development with the synthetic product, obviously they want to see a return on their investment, and rightly so.

The return on the investment for the development of heparin presumably was recouped somewhere back in the 1930s, so that cost is not layered onto the cost of the drug—of a heparin dose; is that correct?

Dr. MEANWELL. Well, I'm interested in the history of these drugs. But—I don't really know what they were sold for in the 1930s, but it wasn't much.

Mr. BURGESS. I don't either.

Well, it's an intriguing process that you are going through. And it's certainly intriguing—heparin, and I guess cortisone, back in the 1930s, was derived from the adrenal gland of an ox, which is a fairly labor-intensive process, I guess, to talk an ox out of its adrenal glands for any length of time. And yet, in the 1940s, Dr. Percy Julian, whom we recognized in the last Congress, we actually gave him an award for recognizing the ability to derive cortisone from a soybean precursor. So it made a big difference.

And just thinking about the juxtaposition of those two compounds, heparin and cortisone, both discovered in the 1930s, cortisone we have got a fairly cheap method of manufacture, ease of manufacture with a synthetic—not a synthetic, but with an easily derived molecule out of the soybean plant. But heparin still had to go through that relatively labor-intensive process that involved talking a pig out of its intestinal mucosa.

Let me—again, I just want to thank you for being here.

One of the other issues that kind of gets obscured in all of this, because we get the heparin active ingredient from the pig mucosa, there are other places where heparin could be—from which it could be derived, and I think you allude to beef lung in your paper. And, in fact, as a medical student, I think that's what I recall learning about with heparin back in the 1970s. But we can no longer do that safely because of preons; is that correct?

Dr. MEANWELL. Yes, sir. I was in a regulatory leadership role in a large drug company at the time when heparin was being sourced from Argentina from cow lungs; and before that, before my time, it was sourced from cow livers. But that had to be stopped because of the risk of mad cow disease. And that was when practically the entire industry switched from bovine cow sources, mainly from South America, to pig sources, mainly from China, as we've heard today.

Mr. BURGESS. Well, again, fascinating subject and fascinating discussion. A good place to end our talk today.

But I appreciate so much you being here and staying with us the entire time. We owe you our gratitude for doing that.

I will yield back, Mr. Chairman.

Mr. STUPAK. Thanks. When was the mad cow disease in Argentina?

Dr. MEANWELL. Well, that would have been in the late 1980s when I was working on that stuff and trying to switch our heparin across to pig sources.

Mr. STUPAK. Let me ask you this: you mentioned the FDA in response to Mr. Burgess' questions, the gold standard; they stand at attention, I think you said, when they come in and do an inspection. And this sort of baffles me.

Baxter said they did their investigation or inspection audit of the plant in 2007. And then, 5 months later, the FDA does theirs, and they found all these problems with the plant.

As I was saying earlier, they were not capable of removing the impurities. They found that they failed to have adequate systems for evaluating both the crude heparin and suppliers of crude heparin. FDA found that test methods performed by SPL had not been verified to assure suitability under actual conditions of use and that the equipment used to manufacture heparin was unsuitable for its intended use.

Could a plant like that deteriorate in 5 months to find all these problems that the FDA finds? Or was—in your opinion, would—they almost always have had to be there, wouldn't they?

Dr. MEANWELL. My opinion, my personal opinion is that that kind of deterioration in 5 months is almost impossible.

Mr. STUPAK. So those problems were there?

Dr. MEANWELL. Pardon me, sir?

Mr. STUPAK. So if it's impossible—so those conditions were always there? They just failed to note them or failed to recognize them?

Dr. MEANWELL. It's difficult for me to answer that, sir, in terms of whether the conditions were always there. But certainly, that kind of deterioration in 5 months is unlikely in a professionally run plant.

Mr. STUPAK. All right. I have no further questions.

Mr. Burgess?

Mr. Shimkus?

There being no further questions, thank you. Thank you for your time and thank you for your insight into this issue. It helps us out.

That concludes all questioning. I want to thank all of our witnesses today for your testimony. And I ask unanimous consent that the hearing record remain open for 30 days for additional questions for the record.

Without objection, the record will remain open.

Mr. STUPAK. I ask unanimous consent that the contents of our document binder be entered into the record.

Without objection, these documents will be entered into the record.

[The information appears at the conclusion of the hearing.]

Mr. STUPAK. That concludes our hearing. Without objection, the meeting of the subcommittee is adjourned.

[Whereupon, at 4:22 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

STATEMENT OF HON. JOE BARTON

Chairman Stupak and Ranking Member Shimkus, thank you for this hearing. The sudden and deadly appearance of contaminated Chinese heparin reminds us why this Subcommittee's investigations and the upcoming legislative work on foreign drug safety are so important.

The heparin contamination appears to have been deliberate, not accidental. Through some complex scientific detective work, FDA has a good idea of exactly how the bad heparin actually caused sickness and death.

This case also demonstrates how and why we need to improve FDA's information technology and the legal and enforcement authorities it needs to prevent future deadly contamination of drugs, especially those made with ingredients that come from abroad. This is something we have to work together on if we are to accomplish the big changes needed.

One of the witnesses at our drug safety hearing last week predicted more heparin-like incidents before the system is fixed. I sure hope not. But realism suggests that it will take more than a few days and some wishes to train new inspectors, fix the information systems, and transform the FDA into an agency that can do the work that we assign to it.

While this is being done, we also know that cheats and connivers don't think or care about the harm they cause, and they won't suddenly stop cheating and start caring. The American market is lucrative for both honest and dishonest manufacturers overseas, and it is all-too-obviously vulnerable to schemes.

FDA is taking positive steps as it develops information sharing agreements with China, which is the source of more and more foreign drug products. This work is a good thing. I don't think—and I don't think FDA thinks—that this is enough. But I'm not certain that FDA knows how much caution is enough, and that worries me.

I believe that we need an FDA focused on the foreign threats. We need an agency that can enforce our standards with speed and reliability at the border.

And we need an agency that pays close attention to the foreign environments where the drugs and their ingredients are produced. The heparin mishap revealed that FDA for several years had a policy of waiving pre-approval inspections for foreign plants if the plants had been previously inspected for other drugs, even in China. That must change.

When the heparin case burst into the news, I recall Chinese officials telling the press that the plant making heparin for export only was not making heparin for the Chinese people. So China didn't check on the plant, and nobody else did, either.

China's attitude seemed to be this: We'll export our product to the United States, but let the buyer beware because we don't care if it is dangerous. A dramatic change in this attitude is needed.

We also have to recognize the central role of industry here. Baxter is not in the business of making people sick. Just the opposite is true. Baxter and other manufacturers have a powerful incentive to make every effort to ensure the safety of its foreign suppliers. We cannot rely on FDA to do everything. The onus is on industry to do its part as well.

Going forward, the FDA and the industry must be proactive and more watchful of the attitudes of the Chinas, the Indias, the other countries with weak safety controls over exports, and act accordingly. If this doesn't happen, we will have more heparin disasters.

I thank the witnesses and hope this hearing can lead to a bipartisan legislative effort to improve the safety of imported drug products.

# # #

STATEMENT OF HON. GENE GREEN

Mr. Chairman, I want to thank you for holding this important hearing today on the heparin disaster. This tragic incident has shown us that the FDA needs more oversight and funding to protect our drug supply.

heparin is a blood thinner derived from pig intestines that is used for surgical procedures and in dialysis. Most of our imported heparin comes from China and 70 percent of this heparin is made in small, unregulated workshops.

Initially, the tainted heparin was believed to be an isolated incident. However, further investigations of the active ingredient in the drug were traced back to a Chinese facility that had never been inspected. This facility was never investigated because the FDA confused the name of the facility with a plant that had a similar name.

The fall out from the contaminated heparin products has stretched far and wide. Tainted heparin has been found in at least 10 countries, not including the United States, and has been linked back to at least 12 different Chinese companies.

It is believed that a man-made chemical is responsible for the many adverse reactions and 81 deaths associated with the drug.

I think we can say with little question that the lack of FDA foreign inspections contributed to the heparin disaster. According to the GAO in FY07, there were 714 drug establishments in China, but only 13 inspections were conducted over the entire year. As another example, India had 410 drug establishments and only 65 inspections were conducted.

What is alarming is the fact that 80 percent of the active pharmaceutical ingredients of drugs consumed in the United States are manufactured abroad and most of those drugs are manufactured in China and India. And, the FDA has publicly acknowledged that some foreign facilities may never be inspected.

In our hearing last week on the FDA foreign drug inspection program, the FDA again admitted they do not have the resources they need to protect our drug supply and they have been slow to request adequate funding from the Administration.

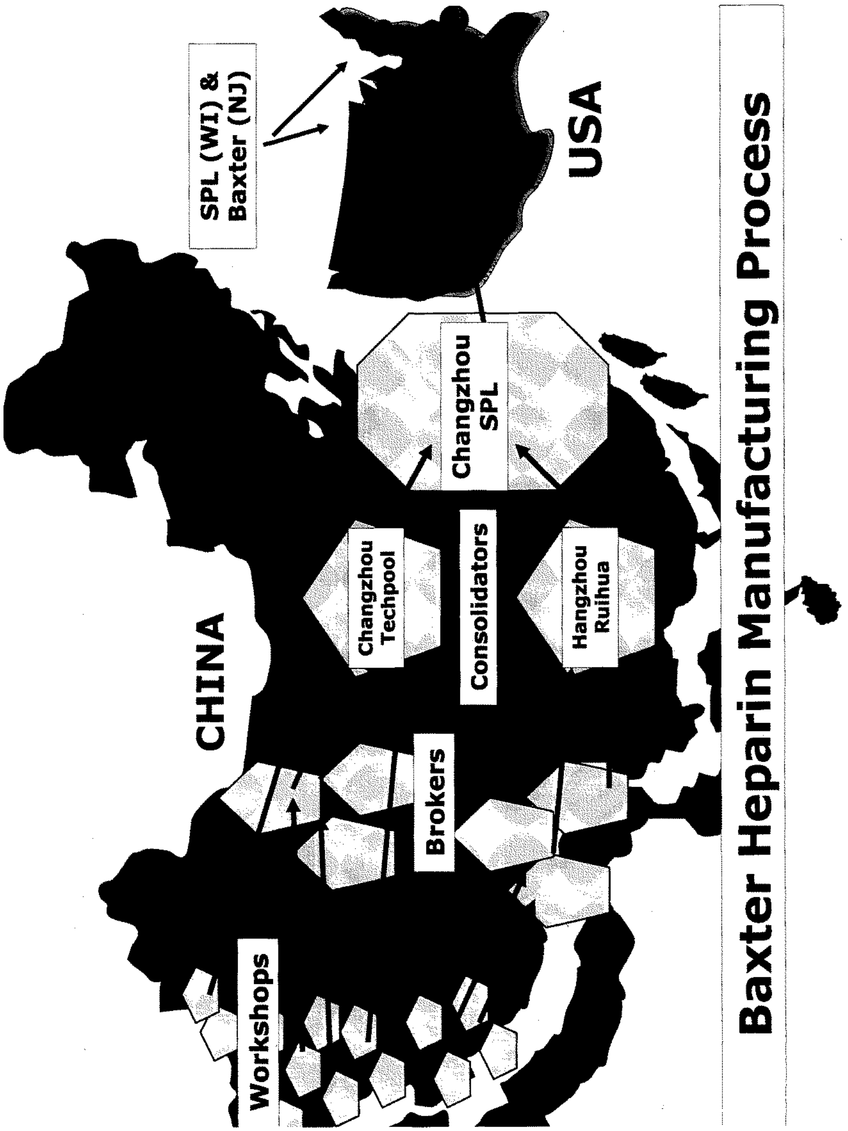
It is clear that congressional intervention is needed to assist FDA with its mission and help protect us from tainted and counterfeit drugs.

In light of the heparin incident and the hearing held in this subcommittee, I signed on as an original cosponsor of Mr. Buyer and Mr. Matheson's bill HR 5839, the Safeguarding America's Pharmaceuticals Act.

This bill a system by which we will be able to track drugs from the time they leave the manufacturing facility to the time they reach patients in the pharmacy, hospital, nursing home, or doctor's office. It would also provide for one, uniform national pedigree system and raise the standards for drug wholesalers while maintaining State's rights to regulate drug wholesalers.

I believe these are important steps that need to be taken to help our pharmaceuticals safe and, I think, relevant to the discussion we will be having today.

Again, thank you Mr. Chairman for holding this hearing and I would like to thank our witnesses for appearing before us today.



Baxter Heparin Manufacturing Process

Average Time Between FDA Inspections

Source: GAO/HEHS-98-21 Foreign Inspection Program

Number of Deaths of Patients Receiving Heparin Reported to FDA, January 1, 2007 through April 13, 2008

Month the Medical Event(s) Occurred	Number of Reported Deaths*	Reported Deaths with One or More Allergic/Hypotensive Symptom(s)
Jan-07	3	1
Feb-07	1	0
Mar-07	4	2
Apr-07	4	2
May-07	2	1
Jun-07	3	2
Jul-07	4	2
Aug-07	1	1
Sep-07	2	2
Oct-07	7	4
Nov-07	11	10
Dec-07	20	13
Jan-08	31	21
Feb-08	28	18
Mar-08	3	0
Unknown date	7	2
Total	131	81

Preapproval Inspection Priorities

1. New molecular entities (NMEs) (includes finished drug product and the active pharmaceutical ingredient)

2. Priority NDAs

3. First application filed by an applicant

4. For-Cause inspection

5. For original applications, if the current CGMP status is unacceptable or greater than 2 years

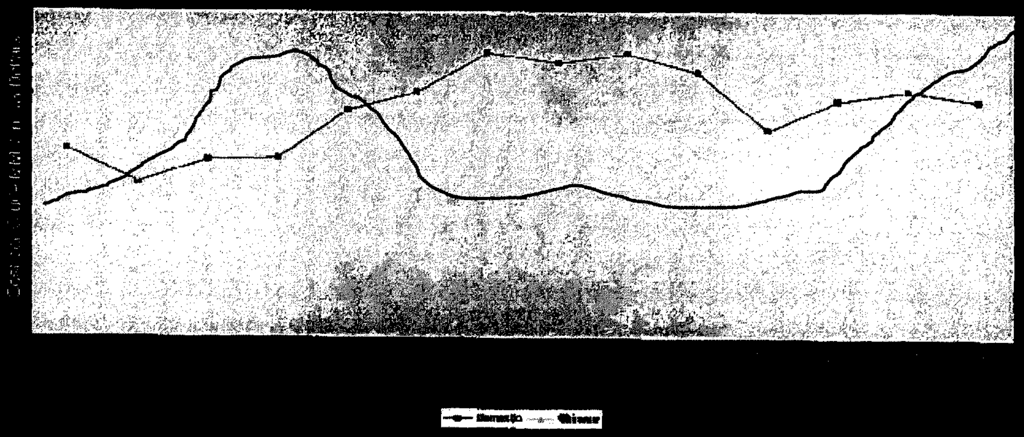
6. For Certain pre-approval supplements, such as site change or major construction, if the CGMP status is unacceptable

7. Treatment IND inspections

8. Information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients

Source: FDA Compliance Program Guidance Manual

Raw Material Cost



Average Cost of Crude Heparin Material

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN - 2 2008

The Honorable Bart Stupak
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

On April 29, 2008, the Food and Drug Administration (FDA) held a hearing entitled "The Heparin Disaster: Chinese counterfeits and American Failures." During that hearing you requested a list of the Chinese companies known to FDA to have been in the supply chain for heparin found to be contaminated (the list is enclosed). Please note that we do not know which of these firms, if any, are the cause of the contamination. It is not clear whether the contamination occurred before, while, or after the products were in the firms' possession. In addition, the fact that a firm is on the list does not mean heparin products from the firm are being shipped, or have been shipped, to the United States (U.S.). Some of the companies on this chart have never shipped heparin to the U.S.

Please be advised that the enclosure includes information received from foreign government counterparts with whom FDA has confidentiality arrangements to not further disclose the information. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information.

We note that the Subcommittee has raised concerns about FDA's ability to protect the American people from contaminated heparin. In fact, FDA has taken comprehensive steps to prevent contaminated heparin from entering the domestic drug market.

Shortly after discovering an increase in adverse reactions to certain heparin sodium products, FDA designed test methods that identified the contaminant (oversulfated chondroitin sulfate or OSCS) and then established and posted on the internet test methods for analyzing heparin for this impurity, *http://www.fda.gov/cder/drug/infopage/heparin/default.htm#screening*. FDA also quickly began on-site inspections and investigations to evaluate the nature and extent of the contamination. FDA inspected both domestic finished dosage form facilities and international active pharmaceutical ingredient (API) suppliers to determine the presence and cause of the contamination, to map the supply route of contaminated products, and to gauge the inspected firms' compliance with current good manufacturing practices (CGMPs).

The API made by one firm, Changzhou-SPL, was associated with a signal of increased adverse events in the U.S. An FDA inspection found significant violations of current good manufacturing practices (CGMP), FDA issued the firm a warning letter, and FDA added the firm to an import alert for firms that have not met CGMPs.

Soon after determining that certain heparin had been contaminated, and even before it had identified the specific contaminant, FDA instituted measures to effectively prevent contaminated heparin from entering the U.S. drug supply. On March 14, 2008, FDA issued a sampling assignment to provide instructions to FDA staff about sampling imported heparin. Under the sampling assignment, all shipments of heparin sodium API are sampled and tested using the methods posted on FDA's website. Some of the testing is conducted by U.S. manufacturers receiving imported heparin products, many of which have made written commitments to FDA that each lot of heparin will be tested for the OSCS. Under the testing commitments, the U.S. firms use FDA's published screening methods and forward their test results within three days to FDA, where the results undergo a two-tiered review. FDA responds with comments and requests for additional information, as appropriate. Under the sampling assignment, if there is not a written testing commitment from a domestic manufacturer FDA tests the heparin API that has been offered for import for OSCS. In addition to sampling and testing, all shipments of heparin sodium API are physically examined upon entry by FDA to verify the security and integrity of the shipment, the nature of the imported product, and the various declarations accompanying the entry (manufacturer, shipper, product description, etc.).

For heparin products other than heparin sodium API, the sampling assignment instructs FDA staff to conduct the reconciliation exam and instructs import reviewers to consult with the appropriate FDA Center, through FDA's Division of Import Operations and Policy, about whether to sample and test the shipment. FDA has ordered sampling and testing of every shipment of crude heparin that has arrived in the U.S. since March 14. FDA's strategy has assured that every declared shipment of heparin sodium API and crude heparin imported since mid-March has been tested for contamination.

Thus, while some of the firms listed may have shipped heparin to the U.S. at some time, FDA has not put any of them on an import alert relating to contaminated heparin. This step is unnecessary because heparin is being effectively stopped at the U.S. border and testing of it for OSCS is being assured. Even if on import alert, the importer would have the opportunity to show the product is compliant, such as by testing for contamination.

FDA believes that, under the circumstances, it has implemented the best approach to protect the public health by having testing conducted by FDA or by a finished dosage form manufacturer that has committed to conduct the testing under circumstances where FDA has sufficient confidence that the firm can appropriately do so. Nonetheless, FDA continues to aggressively gather more information and to monitor the situation to determine whether it should take any different or additional measures to protect the public health.

Beyond testing products upon entry, FDA has inspected and will continue to inspect the firms that supply heparin to the U.S. FDA prioritizes its inspections based on, among other considerations, the need to assure the continued supply of heparin, the participation of U.S. firms in the voluntary testing program, and testing results.

Through all of these actions, FDA has been carefully and diligently taking measures to preserve the availability of medically necessary heparin to U.S. patients and to ensure that the heparin is not contaminated.

Thank you for your interest in this very important matter. We hope that you find the enclosed information useful. If you have any further questions, please let us know.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosure

*Chinese Firms Known To FDA To Have Been In The Supply Chain For Heparin Found To Be Contaminated**

Firm Name	**City**	**Province**
1. Changzhou SPL Co Ltd.	Changzhou	Jiangsu
2. Changzhou Techpool Pharmaceutical	Changzhou	Jiangsu
3. Changsha KEFA New Products Experimental Co., Ltd	Hangzhou	Zhejiang
4. Chongqing Imperial Bio-chem Co., Ltd.	Chongqing	Sichuan
5. Changzhou Qianhong Bio-Pharma Co., Ltd.	Shanghai	
6. Hangzhou Ruihua Biochemical Product	Hangzhou	Zhejiang
7. Nanjing King Friend Biochemical Pharmaceutical Co., Ltd.	Nanjing	Jiangsu
8. Newsmart Chem-Spec Ind. (Trading Firm)	Nantong	Jiangsu
9. Shanghai No.1 Biochemical and Pharmaceutical Co., Ltd.	Shanghai	
10. Shenzhen Hepalink Pharmaceutical Co.	Shenzhen	Guangdong
11. Sichuan Longxin Trading Co., Ltd.	Chengdu	Sichuan
12. Yantai Dongcheng Biochemical Co., Ltd.	Yantai	Shangdong

* Includes shipments from the firms to anywhere in the world. Includes information supplied by foreign governments with whom FDA has confidentiality arrangements to not further disclose the information.

*Note: translation submitted by Arnold and Porter, counsel to SPL.

Invention Application

Application No. 200510045393.9
Publication Date: June 21, 2006
Application Date: December 20, 2005
Applicant: Shandong University
Address: 27 S Shanda Road, Lixia Distriction, Jinan, Shandong 250100 (P. R. China)
Inventor: Shengli Ji, Huifei Cui, Yanqing Chi, Jichao Cao and Fengshan Wang
Agent: Huaqing Zhen; Shengda Patent&Trademark Office, Jinan, Shandong (P. R. China)

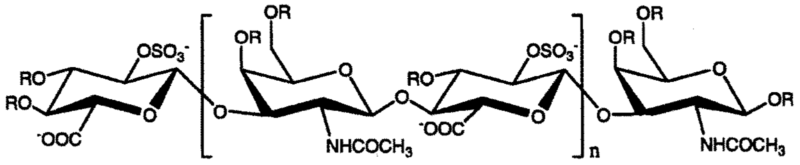
Title: Preparation of Over Sulfated Chondroitin Sulfate

Abstract

This patent introduces an over sulfated chondroitin sulfate (OSCS) which is composed of glucuronic acid derivatives and galactosamine derivatives. It is composed of 2-*O*-sulfo-glucuronic acid-(1→3)-2-*N*-acetyl-2-deoxy-4 (or 6)-*O*-sulfo-galactose. It has an average molecular weight is 1-30 kD and the ratio of sulfo group to carboxyl group is 2~4. This patent also introduces a synthetic method of this OSCS by chemical sulfation of CS. The resulting OSCS inhibits the tumor growth and metastasis, also inhibits mast cell degranulation. Its anticoagulant activity is ≤10 IU/mg. And also it has anti-inflammatory and pain-killing activity.

Claims

1. OSCS contains the derivatives of glucuronic acid and galacotose. It is compose of 2-O-sulfo-glucuronic acid-(1→3)-2-N-acetyl-2-deoxy-4 (or 6)-O-sulfo-galacotose, the structure is:



R: SO_3 or H, n = 1~30

2. In the invention, the oversulfated CS in claim 1 is characterized by: (i) the average molecular weight is 1 kD~30 kD; (ii) the ratio of sulfo group to carboxy group in the molecule is 2~4.
3. In the invention, the preparation of the oversulfate CS in case 1 has the following steps:
    (1) The sulfation of CS: CS was dissolved in water to prepare 15%~30% solution and then the mixture of $HClO_4$ and H_2SO_4 (1:0.05~0.1) was

added to make the final concentration of CS to be 10%~15%. The mixture was stirred at 10~70°C for 2~10 hours and then the organic solvent was added to stop the reaction. The precipitate was collected.

(2) Separation of OSCS: the resulting precipitate in step (1) was dissolved in water and adjusted pH to 7±0.2. Then 4~5 volumes of the organic solvent was added to precipitate OSCS. The precipitate was dissolved in water again, adjusted pH with base to 10±0.2 and heated to 85±2°C and kept changing the air in the reactor and the temperature was kept at 85±2°C for 3±0.5 hours, and then the pH was adjusted to 7 by HCl. 4~5 volumes of the organic solvent was added for desalting and amine-removing. The precipitate was collected.

(3) Purification of OSCS: 10% water solution of the resulting precipitate in step (2) was prepared to do gel chromatography separation and a gradient of 0.01~1 M NaCl solution was used for elution. The fractions with high content of over sulfated CS were collected and then desalted using Sephadex G-10. The product, OSCS, was obtained after lyophilizing.

4. In the invention, a method according to claim 3, characterized in that said the ratio of $HClO_4$ to H_2SO_4 in step (1) is 1:0.05~0.07.
5. In the invention, a method according to claim 3, characterized in that said the temperature of the reaction in step (1) is 30~40°C, and the stirring lasts 4~6 hours.
6. In the invention, a method according to claim 3, characterized in that said the organic solvent in step (1) or (2) is methanol, ethanol, acetone or isopropanol.
7. In the invention, a method according to claim 6, characterized in that said the concentration of ethanol is 95%.
8. In the invention, a method according to claim 3, characterized in that said the resin used in gel chromatography in step (3) is Sephadex G-50, Sephadex G-75, Sephadex G-100 or Superdex-200.
9. In the invention, a method according to claim 8, characterized in that said the gel chromatography used is 3.5×120 cm Sephadex G-75 column.
10. In the invention, a method according to claim 3, characterized in that said the elution buffer in step (3) is 0.2~0.5 M of NaCl solution.

Technical Field

The present invention belongs to biopharmaceutical field, especially describes a novel synthetic method of OSCS.

Background

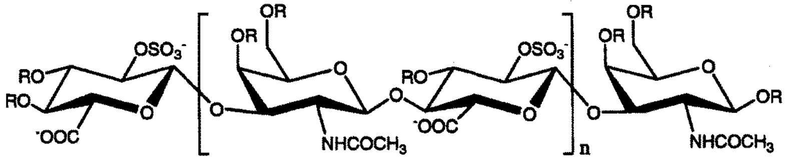
Chondroitin sulfate belongs to the family of sulfated glycosaminoglycans. It has an average molecular weight of 10kD~50kD and it is found exclusively in cartilage of animals.

Much research showed CS can decrease the level of triglyceride and cholesterol in blood and inhibit the formation of atherosclerosis. Petitou and coworkers had reported the chemical sulfation of CS in US patent "Sulfated glycosaminoglycanoid derivatives of the dermatan sulfate and Chondroitin sulfate type" (US patent 5382570), but this technique is very complicated and has high reagent cost which is not suitable for industrial production. Also the resulting product has different structures and activities, which limits its application.

Description

Due to the limitations of the present technique, the invention here introduces a novel preparation method of OSCS. This method uses chemical synthesis to modify the structure of the natural produced CS. The resulting OSCS is a good pain-killer and strong inhibitor of inflammation.

In this invention, the composition of OSCS contains the derivatives of glucuronic acid and galacotose. The molecular is composed of 2-O-sulfo-glucuronic acid-(1→3)-2-N-acetyl-2-deoxy-4 (or 6)-O-sulfo-galacotose and the structure is:



R: SO_3 or H, n = 1~30

In the structure, R is SO_3 or H and n is 1 to 30. The molecular weight is 1 kD~30 kD and the ratio of sulfo group to carboxy group in the molecule is 2~4.

This preparation method of OSCS described includes the following steps:

(1) The sulfation of CS: CS was dissolved in water to prepare 15%~30% solution and then the mixture of $HClO_4$ and H_2SO_4 (1:0.05~0.1) was added to make the final concentration of CS to be 10%~15%. The mixture was stirred at 10~70°C for 2~10 hours and then the organic solvent was added to stop the reaction. The precipitate was collected.

(2) Separation of OSCS: the resulting precipitate in step (1) was dissolved in water and adjusted pH to 7±0.2. Then 4~5 volumes of the organic solvent was added to precipitate OSCS. The precipitate was dissolved in water again, adjusted pH with base to 10±0.2 and heated to 85±2°C and kept changing the air in the reactor and the temperature was kept at 85±2°C for 3±0.5 hours, and then the pH was adjusted to 7 by HCl. 4~5 volumes of the organic solvent was added for desalting and amine-removing. The precipitate was collected.

(3) Purification of OSCS: 10% water solution of the resulting precipitate in step (2) was prepared to do gel chromatography separation and a gradient of 0.01~1 M NaCl solution was used for elution. The fractions with high content of oversulfated CS were collected and then desalted using Sephadex G-10. The product, OSCS, was obtained after lyophilizing.

In the preparation method of OSCS described above, the best ratio of $HClO_4$ to H_2SO_4 in step (1) is 1:0.05~0.07.

In the preparation method of OSCS described above, the best reaction temperature in step (1) is 30°C ~ 40°C and the best stirring time is 4~6 hours.

In the preparation method of OSCS described above, the organic solvent in step (1) or (2) is methanol, ethanol, acetone or isopropanol. The best organic solvent is 95% ethanol. In the preparation method of OSCS described above, the gel chromatography in step (3) is using Sephadex G-50, Sephadex G-75, Sephadex G-100 or Superdex-200. The best separation is obtained by using 3.5×120 cm Sephadex G-75 column.

In the preparation method of OSCS described above, the best elution buffer in step (3) is 0.2~0.5 M of NaCl solution.

This preparation method of OSCS described above has the advantages of following: (i) the technique used is simply; (ii) the cost of reagents used is low; (iii) there are fewer requirements for the production environment and instrument; and (iv) the resulting product has high purity, which is suitable for industry production.

The OSCS obtained from this method has anti-inflammatory and pain-killing activity. Experiments showed its anticoagulant activity is ≤10 IU/mg and it inhibits the tumour growth and metastasis and mast cell degranulation.

Next, the detail of this invention is described using a practice example.

Practice 1:

(1) The sulfation of CS: 100 g of native CS (commercial available) was dissolved in water to prepare 20% solution and then the mixture of $HClO_4$ and H_2SO_4 (1:0.05) was added to make the final concentration of CS to be 10%. The mixture was stirred at 35°C for 5 hours and then 4000 ml of absolute ethanol was added to stop the reaction. The precipitate was collected.

(2) Separation of OSCS: the resulting precipitate in step (1) was dissolved in 1000 ml of water and pH was adjusted to 7 by 20% NaOH. Then 4 volumes of 95% ethanol were added for precipitation. The resulting precipitate was re-dissolved in water to prepare 10% solution, pH was adjusted to 10 by 20% NaOH and heated to 85°C and kept for 3 hours, then pH was adjusted to 7 by 6M HCl. 4 volumes of 95% ethanol was added for desalting and amine-removing. The precipitate was collected.

(3) Purification of OSCS: 10% water solution of the precipitates obtained in step (2) was loaded onto 3.5×120 cm Sephadex G-75 column and eluted using a gradient of 0.2 M NaCl solution. The fractions with high content of OSCS were collected and then desalted using Sephadex G-10. The product, OSCS, was obtained after lyophilizing.

The molecular weight, structure and anticoagulantory activity of OSCS obtained were determined.

Practice 2:

(1) The sulfation of CS: 200 g of native CS (commercial available) was dissolved in water to prepare 30% solution and then the mixture of $HClO_4$ and H_2SO_4 (1:0.07)

was added to make the final concentration of CS to be 10%. The mixture was stirred at 40°C for 6 hours and then 4000 ml of absolute ethanol was added to stop the reaction. The precipitate was collected.

(2) Separation of OSCS: the resulting precipitate in step (1) was dissolved in 1000 ml of water and pH was adjusted to 7 by 20% NaOH. Then 4 volumes of 95% methanol were added for precipitation. The resulting precipitate was re-dissolved in water to prepare 10% solution, pH was adjusted to 10 by 20% NaOH and heated to 85°C and kept for 3.5 hours, then pH was adjusted to 7 by 6M HCl. 4 volumes of 95% methanol was added for desalting and amine-removing. The precipitate was collected.

(3) Purification of OSCS: 10% water solution of the precipitates obtained in step (2) was loaded onto 3.5×120 cm Sephadex G-100 column and eluted using a gradient of 0.5 M NaCl solution. The fractions with high content of OSCS were collected and then desalted using Sephadex G-10. The product, OSCS, was obtained after lyophilizing.

Practice 3:

(1) The sulfation of CS: 100 g of native CS (commercial available) was dissolved in water to prepare 25% solution and then the mixture of $HClO_4$ and H_2SO_4 (1:0.09) was added to make the final concentration of CS to be 10%. The mixture was stirred at 30°C for 10 hours and then 4000 ml of acetone was added to stop the reaction. The precipitate was collected.

(2) Separation of OSCS: the resulting precipitate in step (1) was dissolved in 1000 ml of water and pH was adjusted to 7 by 20% NaOH. Then 4 volumes of acetone were added for precipitation. The resulting precipitate was re-dissolved in water to prepare 10% solution, pH was adjusted to 10 by 20% NaOH and heated to 85°C and kept for 3 hours, then pH was adjusted to 7 by 6M HCl. 4 volumes of acetone was added for desalting and amine-removing. The precipitate was collected.

(3) Purification of OSCS: 10% water solution of the precipitates obtained in step (2) was loaded onto 3.5×120 cm Sephadex G-50 column and eluted using a gradient of 0.8 M NaCl solution. The fractions with high content of OSCS were collected and then desalted using Sephadex G-10. The product, OSCS, was obtained after lyophilizing.

[illegible]	[illegible]	[illegible]
	[illegible]	
1	Letter to FDA Commissioner von Eschenbach from Chairmen Dingell and Stupak, re: Wall Street Journal article on foreign drug inspections.	02/14/2008
2	FDA Response letter to Chairman Dingell, re: February 14, 2008 correspondence.	04/24/2008
3	Letter to FDA Commissioner von Eschenbach from Chairmen Dingell and Stupak, re: FDA's drug approval policy regarding pre-approval inspections.	02/21/2008
4	Letter to Robert Parkinson (Baxter) from Chairmen Dingell and Stupak, re: Heparin production.	02/21/2008
5	Baxter Response to Committee Staff, re: February 21, 2008 correspondence.	03/04/2008
6	Letter to HHS Secretary Michael Leavitt from Chairmen Dingell and Stupak, re: FDA preapproval inspection policy.	02/21/2008
7	Letter to David Strunce (SPL) from Chairmen Dingell and Stupak, re: February 28, 2008 recall of Heparin.	03/12/2008
8	SPL Response to Committee Staff, re: March, 12, 2008 correspondence.	03/18/2008
9	SPL Response to Committee Staff, re: March, 12, 2008 correspondence.	04/02/2008
10	Letter to FDA Commissioner von Eschenbach from Reps. Dingell, et al, re: Heparin-Chinese drug facility inspections.	03/19/2008
11	Email Correspondence from Stephen Mason to David Nelson, et al, subject: "Follow up Questions." (with attachments)	03/05/2008
	[illegible]	
12	Email correspondence from David Horowitz to Deborah Autor, et al, re: "Inspections of 'Immediate Public Health Impact'," related to preapproval policy.	03/31/2003
13	Recall Press Release, re: "Baxter Issues Urgent Nationwide Voluntary recall of Heparin..."	01/25/2008
14	"Questions and Answers on Heparin Sodium Injection (Baxter)."	02/11/2008
15	Media Transcripts, "Transcripts of FDA Press Conferences on Adverse Events Associated with Baxter Healthcare Corporation's Multiple-Dose Vials of Injectable Heparin." (Index only, full transcripts contained in Committee files)	02/11/2008 - 03/19/2008
16	FDA Form 483 provided to Yan Wang, Changzhou SPL	Feb. 2008
17	Changzhou SPL Co., Ltd. Response to Form FDA 483	03/17/2008
18	Establishment Inspection Report (EIR), Changzhou SPL Company, Ltd. (Committee may revise if company redactions are excessive)	02/26/2008
19	Establishment Inspection Report, Changzhou Techpool Pharmaceutical Co.	02/27/2008

20	Establishment Inspection Report, Hangzhou Ruihua Biochemical Products Co., Ltd.	02/28/2008
21	FDA Public Health Update, re: "Recall of Heparin Sodium Injection and Heparin Lock Flush Solution (Baxter)."	02/28/2008
22	Recall Press Release, re: "Baxter to Proceed with Recall of Remaining Heparin Sodium Vial Products."	02/28/2008
23	"Information on Heparin Sodium Injection."	03/06/2008
24	Recall Press Release, re: "American Health Packaging Announces a Recall of Approximately 1400 Units of Heparin Sodium Vial Products as Part of Broader Baxter Recall."	03/20/2008
25	Recall Press Release, re: "B. Braun's Supplier Recall of Heparin API Prompts Voluntary Recall of Heparin Solution."	03/21/2008
26	Recall Press Release, re: "Covidien Initiates Voluntary Recall of Pre-Filled Syringes Containing Heparin."	03/28/2008
27	FDA Warning Letter to Dr. Yan Wang (Changzhou SPL Company) from FDA Office of Compliance, CDER, re: review of the EIR for the SPL facility in Changzhou.	04/21/2008
28	"Preapproval Inspection Priorities."	
29	"Number of Deaths of Patients Receiving Heparin Reported to FDA."	
	[illegible]	
30	Audit report for the cGMP audit of Changzhou SPL, China	09/20/2007
31	Baxter Response to September 20, 2007 audit	02/26/2008
	[illegible]	
32	Invention Application, "Preparation of Over Sulfated Chondroitin Sulfate."	12/20/2005
33	United States Patent 5382570, American Patent in reference to Chinese Patent.	
	[illegible]	
34	SPL Presentation to Subcommittee Staff	03/20/2008
	[illegible]	
35	FDA Medwatch, subject: "Heparin Sodium Injection, Serious Adverse Events Reported in Patients Receiving Bolus Doses of Medication."	02/11/2008
36	Wall Street Journal (WSJ) article by Thomas M. Burton, et al, subject: "Heparin Probe Finds U.S. Tie to Chinese Plant."	02/15/2008
37	Los Angeles Times article by Don Lee, et al, subject: "Plant in China Under Scrutiny."	02/20/2008
38	WSJ Health Blog article by Jacob Goldstein, subject: "China Washes Hands on Heparin Purity."	02/27/2008
39	Los Angeles Times article by Ricardo Alonso-Zaldivar, subject: "Look-alike Drug May Have Tainted Heparin	03/06/2008

40	WSJ article by Anita Greil, et al, subject: "German Firm Recalls Heparin with China Link."	03/07/2008
41	Associated Press (AP) article, subject: "China Orders Tighter Controls on Production of Heparin."	03/21/2008
42	WSJ article by Jeanne Whalen, et al, subject: "Three More European Countries Recall Heparin."	03/26/2008
43	Outsourcing-pharma.com article by Kirsty Barnes, subject: "China Watchdog Responds to Heparin Scare."	03/30/2008
44	New York Times (NYT) article by Walt Bogdanich, subject: "The Drug Scare that Exposed a World of Hurt."	03/30/2008
45	Mercury News editorial, subject: "We Can't Afford FDA Bungling on Pharmaceuticals."	04/03/2008
46	Washington Post article by Marc Kaufman, subject: "Rise in Price was a Sign of Trouble."	04/13/2008
47	The Canadian Press article, subject: "Heparin Probe Highlights Challenges of Regulating Global Drugs Market."	04/13/2008
48	Washington Post article by Marc Kaufman, subject: "U.S. and China Dispute Conclusions About Tainted Heparin."	04/21/2008
49	Chicago Tribune article by Bruce Japsen, subject: "FDA: Heparin Supplier's Chinese Factory 'Unsuitable'."	04/21/2008
50	NYT article by Gardiner Harris, subject: "U.S. Identifies Tainted Heparin in 11 Countries."	04/22/2008
51	WSJ article by Alicia Mundy, et al, subject: "U.S., China Clash Over Heparin."	04/22/2008
	[illegible]	
52	Carbohydrate Research, "Chemical Sulfation of Preparations of Chondroitin 4 and 6-Sulfate, and Dermatan Sulfate. Preparation of Chondroitin Sulfate E-Like Materials from Chondroitin 4-Sulfate," vol. 158, pp. 183-190.	1986
53	Carbohydrate Research, "Conformational Changes and Anticoagulant Activity of Chondroitin Sulfate Following its O-sulfonation," vol. 306, pp. 35-43.	1998
54	Nature Biotechnology, "Oversulfated Chondroitin Sulfate is a Contaminant in Heparin Associated with Adverse Clinical Events."	April 2008
55	New England Journal of Medicine, "Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System."	April 2008

ONE HUNDRED TENTH CONGRESS
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

February 14, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

A recent disclosure in the Wall Street Journal alleges that a Chinese facility that has not been inspected by the Food and Drug Administration (FDA) produced the active ingredient in a widely used Baxter International, Inc. blood-thinning drug that has recently been associated with hundreds of adverse events, including four deaths.

While it is neither clear from the article nor from initial conversation with your staff if this plant is the source of the cause of the over 350 adverse reactions, we find it remarkable that the Wall Street Journal article reports that the FDA has publicly admitted they never inspected the Chinese facility that made the active ingredient in the Baxter drug due to "human error and inadequate information technology systems."

Throughout this past year, we have repeatedly raised concerns with you regarding the disastrous state of your agency's foreign inspection program related to pharmaceuticals manufactured abroad. These problems included a lack of resources and antiquated information technology (IT) systems that are used to track foreign firms making products destined for the United States. For example, in a recent hearing we heard testimony that the IT system used by FDA to specifically manage this program was found to be archaic and contained significant inaccuracies that directly affected the agency's ability to prioritize inspections.

As was reported by the U.S. Government Accountability Office (GAO) in that same hearing, FDA could not tell with certainty how many foreign firms were subject to inspection, or even where they were located. One database, for example, reported approximately 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while a separate database reported almost 7,000 foreign establishments that appeared to have shipped drugs into the U.S. that same year. To date, FDA has not reconciled this difference. Given the FDA's antiquated computer monitoring system and their inability to easily access reliable data, we are not surprised that FDA cannot say with precision when or if this firm was inspected.[1]

The matter of resources to conduct inspections was a particularly troubling aspect of our investigation. Both the Committee's own investigation and the audit by GAO found that FDA's resources were completely inadequate for inspecting foreign firms with meaningful frequency. While current law requires that FDA inspect a U.S. domestic firm making a drug product for the U.S. market once every 2 years, GAO found that FDA had only enough resources to inspect foreign firms on average once every 13 years. For China alone—now one of the largest producers of drug product for the U.S. market and the partner in these recently-signed agreements—FDA has only been able to inspect between 10 and 20 firms each year against a backlogged inventory of more than 700 firms (which are only growing in number). At this rate, FDA can only inspect a Chinese firm exporting drug products to the U.S. once every 40 to 50 years.[2]

A lack of resources regarding foreign drug inspections and the problems with the agency's IT systems used to track manufactures and imports was also pointed out to you by your own Science Advisory Board review. Recall that in December 2006, you requested that this internal advisory group form a special subcommittee to assess whether "science and technology" at the agency was capable of supporting existing and future regulatory operations at FDA. A scathing report entitled *"FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology"* was produced and concluded that FDA was dangerously underfunded and was unable to pursue core regulatory missions, thus placing American lives at risk. This report was the main topic of a hearing just last month before the Subcommittee where you also appeared. Each of the witnesses who testified on behalf of this study noted that your agency was failing, and that your agency's ability to safeguard both the food and drug supply was a considerable and growing risk. Regarding drug inspections, the report's language was particularly stark:

> "Although approximately 80 percent of the active pharmaceutical ingredients used in our prescription drugs are imported from abroad, and foreign imports of drugs and active pharmaceutical ingredients were valued at more than $42 billion in 2006, FDA conducted only 361 foreign drug and biological product establishments in 2006. Only 32 Field inspections were made in India and 15 in China, the two largest sources of

---

[1] U.S. Government Accountability Office, Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturer. Statement of Marcia Crosse, Director Health Care, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 1, 2007.

[2] Id.

> pharmaceutical exports to the United States. *Millions of shipments of FDA-regulated products are imported into the country each year from foreign facilities that have never been inspected by FDA and, with current appropriations, never will be* [emphasis added]."[3]

We have had countless conversations with you regarding your agency's inability to adequately inspect the Nation's drug supply, particularly those sources that are increasingly originating from abroad and from areas lacking robust regulatory regimes. Conversations and related hearings on this matter, the findings of the GAO, and those findings of your own Science Board, however, appear to go unheeded.

There is little material indication through the President's 2009 budget request or recent actions at the agency, which would lead us to believe you are making the needed changes to safeguard the public from these growing threats. GAO spoke to this matter directly in testimony heard by you at the November 1, 2007, hearing regarding FDA's foreign drug inspection program: "[U]ntil FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized, and safe."[4] Clearly to date, you have been unable to assure the public these products are safe because you have been unable to competently address the systemic weaknesses in this program identified by GAO, the Science Board, and this Subcommittee. Because of such inaction, American lives are unnecessarily being placed at risk.

Therefore, we request that you provide the Committee with the following information, specifically regarding the drug Heparin, and in general the foreign inspection program:

1. All inspection reports related to the Chinese company that Baxter International Inc. was apparently using to produce Heparin (e.g., all FDA form 483s);

2. A complete timeline of inspections for each of these facilities;

3. An explanation as to why this plant may have been allowed to ship drug products into the U.S. without a formal GMP preapproval or surveillance inspection;

4. A detailed explanation as to what steps FDA is currently taking regarding all active ingredients from this plant;

---

[3] "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," Prepared for FDA Science Board, November 2007, B-22.

[4] U.S. Government Accountability Office, Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturer. Statement of Marcia Crosse, Director Health Care, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 1, 2007, p. 22

5. A detailed explanation about how the President's fiscal year 2009 budget will materially change the inspection frequency regarding foreign inspections now conducted, on average, once every 13 years;

6. For Baxter and every other manufacturer of the finished dosage form, please supply all pages of the NDA, ANDA, or related documents wherein FDA has been notified of the raw material suppliers, all documents wherein FDA has concurred with the choice of any supplier or a change in the choice of supplier;

7. All inspection reports of manufacturers of Heparin for the past five years;

8. All documents in the Data Master Files or elsewhere relating to FDA approval of raw material suppliers of the active ingredient in Heparin.

Thank you for your attention to this matter. We would ask that you provide this information on a rolling basis to the Subcommittee as soon as possible, but no later than February 22, 2008. If you have any questions on this matter, please have your staff contact Christopher Knauer or David Nelson with the Committee on Energy and Commerce staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 24 2008

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of February 14, 2008, co-signed by Chairman Bart Stupak, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, requesting information and documents regarding the drug Heparin and the Food and Drug Administration's (FDA or the Agency) foreign inspection program. We have sent partial responses on February 27 and March 5, 2008. This is a further partial response.

Information contained in the enclosures may include information that is trade secret, commercial confidential or other information protected from disclosure to the public under the Freedom of Information Act (Title 5, *United States Code* [U.S.C.] 552), the Trade Secrets Act (18 U.S.C. 1905), the Privacy Act (5 U.S.C. 552a), and FDA regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information.

We have repeated your question below in bold followed by our response.

3. **An explanation as to why this plant may have been allowed to ship drug products into the U.S. without a formal GMP preapproval or surveillance inspection.**

Changzhou Scientific Protein Laboratories (Changzhou SPL) was able to ship heparin sodium active pharmaceutical ingredient (API) into the United States because the API was the subject of a new drug application (NDA) from Baxter International, Inc. (Baxter) that FDA approved in 2004. The Center for Drug Evaluation and Research (CDER) approved Baxter's NDA for heparin API without a pre-approval inspection of Changzhou SPL as a result of human error. FDA staff entering data into a database mistakenly selected the name of another manufacturing facility instead of Changzhou SPL. The facility selected had a satisfactory inspectional history; FDA had inspected this facility three times prior to 2004 and had found the facility to be in compliance with current good manufacturing practices (cGMP). Therefore, in accordance with CDER policy, the CDER Office of Compliance (OC) determined that the NDA could be approved without a pre-approval inspection. Had the proper facility (Changzhou SPL) been identified in the system, FDA would have conducted an inspection of this site.

4. **A detailed explanation as to what steps FDA is currently taking regarding all active ingredients from this plant.**

We are no longer importing heparin sodium API manufactured by Changzhou SPL. An Import Alert was issued on March 10, 2008, for "Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs." Further, Scientific Protein Laboratories (SPL) of Waunakee, Wisconsin, a partial owner of Changzhou SPL, initiated a voluntary recall of all of its heparin sodium API of Chinese derivation. This API was used primarily in drug products but also in some medical devices. SPL's recall covered all possible users of this API, primarily in drug products and also some medical devices, which have in turn conducted recalls of finished products using these ingredients. There were other recalls of finished pharmaceuticals, that were previously manufactured, that used these APIs. Further recalls were not of APIs but of finished dosage forms. FDA inspected the Changzhou and United States SPL facilities in Waunakee, Wisconsin; collected and analyzed numerous samples in conjunction with various academic institutions; and reviewed many of the results of analytical work done by SPL, Baxter, and other entities. This collaborative work led to the identification of the contaminant, over-sulfated chondroitin sulfate, and FDA's release of information about two tests that manufacturers and regulators can use to screen for the contaminant. Our investigation into the source of this contaminant is ongoing.

Further, on March 10, 2008, FDA added Changzhou SPL to the list of firms and pharmaceuticals that are subject to import detention without physical examination. This Import Alert covers all heparin from Changzhou SPL, including API intended for both possible use as a component in drug products or medical devices. Although FDA has no information that Changzhou SPL is manufacturing medical devices, medical device product codes are included in the Import Alert in the event of potential miscoding of import entries. Refer to the attachment of Import Alert 66-40, "Detention Without Physical Examination of Drugs from Firms Which Have Not Met Drug GMPs" which is available at *http://www.fda.gov/ora/fiars/ora_import_ia6640.html.*

5. **A detailed explanation about how the President's fiscal year 2009 budget will materially change the inspection frequency regarding foreign inspections now conducted, on average, once every 13 years.**

The fiscal year (FY) 2009 program level budget request for FDA's Human Drugs Program is $738.7 million. The program level budget includes budget authority and user fees. This amount represents a proposed Human Drugs Program increase of $58.5 million from the FY 2008 enacted appropriation.

Of the $738.7 million for the Human Drugs Program, the allocation for field activities conducted by the Office of Regulatory Affairs (ORA) in the Human Drugs Program is $99.5 million. This amount represents a proposed increase for field activities of $5.4 million compared to FY 2008. The $5.4 million includes budget authority increases, user fee increases, and administrative savings.

Of the $5.4 million, $1.256 million is targeted for ORA's Office of Criminal Investigations (OCI). This amount will increase the ability of OCI to investigate criminal import violations. The volume of drugs imported into the United States is estimated to increase by 12 percent during FY 2009. This increase in volume heightens the need for OCI investigators to investigate criminal import violations.

The budget also includes $1.9 million for the annual pay inflation adjustment for ORA employees assigned to the Human Drugs Program. The $5.4 million will not increase the frequency of foreign inspections.

In the FY 2007 Revised Continuing Resolution, Congress provided increased funds that allowed ORA to hire new investigators. In FY 2007, ORA hired 104 new investigators across all field program areas. These new investigators were quickly able to perform routine ORA inspections. As a result of the inspections conducted by the new investigators, more experienced investigators became available to conduct more complex inspections, such as foreign drug inspections. The table below displays the increases in foreign inspections that FDA anticipates as a result of our hiring new investigators. This table is a component of the table that appears on page 97 of our FY 2009 budget justification.

PROGRAM OUTPUTS- IMPORT/FOREIGN INSPECTIONS	**FY 2008 Estimate**	**FY 2009 Estimate**
Foreign Pre-Approval Inspections (NDA) incl the President's Emergency Plan for AIDS Relief (PEPFAR)	192	192
Foreign Pre-Approval Inspections (ANDA) incl PEPFAR	92	187
Foreign Bioresearch Monitoring Program Inspections incl PEPFAR	46	57
Foreign Drug Processing (GMP) Program Inspections	221	281
Foreign Adverse Drug Events Project Inspections	16	16
Total Above Foreign FDA Inspections	567	733

6. **For Baxter and every other manufacturer of the finished dose form, please supply all pages of the NDA, ANDA, or related documents wherein FDA has been notified of the raw material suppliers, all documents wherein FDA has concurred with the choice of any supplier or a change in the choice of supplier.**

Documents responsive to this request are enclosed as TAB A.

8. All documents in the Data Master Files or elsewhere relating to FDA approval of raw material suppliers of the active ingredient in Heparin.

Documents responsive to this request are enclosed as TAB B.

Thank you again for your interest in this matter. If you have any further questions, please let us know. A similar letter without the enclosures has been sent to Chairman Stupak.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosures

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

ONE HUNDRED TENTH CONGRESS
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

February 21, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
5600 Fisher Lane, Room 1555
Rockville, MD 20857

Dear Dr. von Eschenbach:

We are seeking clarification of what appears to be a change in the Food and Drug Administration's (FDA) drug approval policy regarding pre-approval inspections. On February 15, 2008, the Committee on Energy and Commerce staff interviewed your staff regarding the ongoing concerns with Baxter International's manufactured blood-thinning drug Heparin. Your staff confirmed that the Chinese plant that provides the active pharmaceutical ingredient for Heparin had never been inspected by FDA, despite the policy of pre-approval inspections that has been followed by Administrations for nearly two decades.

In addition, FDA staff acknowledged that there is no statutory requirement for a pre-approval inspection before a firm begins shipping drug product to the United States, but rather it is FDA policy to conduct such an inspection. We were further informed that FDA is under no obligation to withhold approval or otherwise bar shipment until such an inspection is completed. Most importantly, your staff advised that selling a drug product from a plant that has never undergone a pre-approval inspection does not constitute the distribution of an unapproved drug.

If FDA has abandoned, either formally or informally, its vital pre-approval inspection policy for the U.S. drug supply, this represents a troubling development that puts consumers at risk. For a drug to be eligible for approval by FDA, it has been the understanding of Congress that the agency must approve each step of drug manufacturing, including all ingredient sources. We understood that a pre-approval inspection was accomplished through a formal physical visit of the facility to ensure it meets current Good Manufacturing Practices. This understanding is shared by the Government Accountability Office, who recently testified at a hearing before the Subcommittee that:

> "Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug product. Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications and ensures that the manufacturer of the finished drug product, as well as each manufacturer supplying a bulk drug substance used in the finished product, manufactures, processes, and packs the drug adequately to preserve its identity, strength, quality, and purity."

The need for such inspections was highlighted more than 20 years ago after this Committee exposed similar problems with the generic drug industry. Preapproval inspections were designed to assure that drug manufacturers would never again be able to gain FDA approval by asserting that drugs would be produced pursuant to a valid manufacturing process and with qualified suppliers of ingredients when the facility was incapable of manufacturing the drugs as specified. Apparently, FDA has deliberately failed to apply this inspection policy to drug manufacturers in China.

Accordingly, we request that you provide to us a written clarification of FDA's current policy for preapproval inspections. Further, we ask that you make available Dr. Janet Woodcock, Margaret Glavin, and those reviewers responsible for the approval of the active ingredient supplier for the Heparin now under scrutiny by your agency, for briefings with Committee staff.

We ask that you please respond to this letter and assure that the requested briefings are concluded prior to Friday, February 22, 2008. If you have any questions, please have your staff contact David Nelson or Chris Knauer with the Committee on Energy and Commerce staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

February 21, 2008

Mr. Robert L. Parkinson, Jr.
Chairman of the Board, Chief Executive Officer and President
Baxter International Inc
One Baxter Parkway
Deerfield, IL 60015-4625

Dear Mr. Parkinson:

A recent disclosure in the Wall Street Journal alleges that a Chinese facility that has not been inspected by the Food and Drug Administration (FDA) produced the active ingredient in Heparin, a widely used blood-thinning drug manufactured by Baxter International, Inc., which has recently been associated with over 350 adverse events, including 4 deaths. While it is not clear from the article whether this plant is the source of the problem that caused the adverse reactions and deaths, we are troubled by the possibility that Baxter has been selling a drug with an active ingredient that has never been approved. We have asked FDA to explain a claim made by its press office that FDA had never inspected the Chinese facility, which made the active ingredients in the Baxter drug, due to "human error and inadequate information technology systems."

The key question that Baxter must answer is this: Was your firm mislead by FDA into believing that the Chinese firm was an approved supplier of an active ingredient for Heparin? If not, then we are concerned that your company was knowingly distributing an unapproved drug.

In order for us to properly evaluate the relative roles of the FDA and Baxter in this tragedy, we request that you supply all records (the terms records and relating to are defined in the attachment to this letter) since January 1, 2002, relating to:

1. Suppliers of active ingredients for the drug Heparin;
2. Inspection documents such as 483s and EIRs for all Baxter manufacturing facilities that produce Heparin or any intermediates used in the production of Heparin;

3. Correspondence with FDA or other regulatory bodies inside or outside the United States relating to Heparin;

4. Promotional or marketing materials relating to Heparin, including but not limited to documents that discuss the pricing policies for this drug;

5. All due diligence performed on Heparin and/or the facilities used to manufacture the drug or its intermediates;

6. Recalls of the drug or requests to recall the drug;

7. All adverse events reports associated with Heparin whether or not such reports were forwarded to FDA or other regulatory bodies.

Please send your response and supply the requested documents within two weeks of the date of this letter. If you have any questions regarding these requests, please contact David Nelson or Chris Knauer with the Committee on Energy and Commerce staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

KING & SPALDING

King & Spalding LLP
1700 Pennsylvania Avenue, N.W.
Washington, DC 20006-4706
www.kslaw.com

Theodore M. Hester
Direct Dial: (202) 626-2901
thester@kslaw.com

March 4, 2008

BY HAND DELIVERY
ATTN: Mr. David Nelson

The Honorable John D. Dingell, Chairman
Committee on Energy and Commerce
The Honorable Bart Stupak, Chairman
Subcommittee on Oversight and Investigations
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Dingell and Chairman Stupak:

Baxter International Inc. ("Baxter") has asked me to advise you that the information contained in tabs E, F, and I of the letter being transmitted herewith may contain confidential information that could be subject to a confidentiality agreement with Scientific Protein Laboratories, LLC ("SPL"). SPL has requested that the Committee treat these attachments as confidential. SPL believes these materials contain confidential and/or commercially valuable and proprietary business information and trade secrets. SPL requests that the Committee keep this material confidential and limit access to Members and staff involved in this inquiry. SPL also requests return of these attachments when the Committee has completed its review. These attachments can be returned to counsel for SPL, Mr. Daniel Kracov, Arnold & Porter, 555 Twelfth Street, NW, Washington D.C. 20004.

If you have any questions regarding this matter, or need additional information, please do not hesitate to call me at (202) 626-2901.

Sincerely,

Theodore M. Hester

Peter J. Arduini
Corporate Vice President
President, Medication Delivery

Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois 60015

847.948.4175
Fax: 847.948.4177
peter_arduini@baxter.com
www.baxter.com

Baxter

March 4, 2008

DELIVERY BY HAND VIA MESSENGER

The Honorable John Dingell, Chairman
United States House of Representatives
Committee on Energy and Commerce
c/o Mr. David Nelson
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Bart Stupak, Chairman
United States House of Representatives
Subcommittee on Oversight and
Investigations
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Dingell and Chairman Stupak,

I am the President of the Medication Delivery business of Baxter Healthcare Corporation ("Baxter"). Robert Parkinson, Chairman and CEO of Baxter, has asked that I provide you on Baxter's behalf an update on the status of our heparin recall and root cause investigation, and a preliminary response to your letter to him dated February 21, 2008. It is an honor to speak on behalf of Baxter. I assure you that Baxter's first priority is ensuring that its products are safe, and that Baxter is in pursuit of the root cause of the increase in the allergic-type reactions associated with its heparin product, and is committed to making sure this critical product is available for all of the patients that need it across the United States.

Baxter

By way of background, Baxter is a healthcare company with a proud 75-year history of manufacturing therapies for patients with the most critical health needs. We assist healthcare professionals and their patients with treatment of some of the most complex medical conditions including hemophilia, immune disorders, kidney disease and cancer. Baxter applies its expertise in medical devices, biotechnology and pharmaceuticals to make a meaningful difference in patients' lives. We employ over 17,000 employees in the United States, with over 11,000 of those people in manufacturing jobs. Our Cherry Hill, New Jersey facility, which manufactures our heparin injectable product, employs approximately 800 people.

Heparin

Heparin is an anticoagulant that has been used for over 70 years and is one of the most commonly used therapies in the United States. It is administered to millions of patients each year in a wide variety of clinical and surgical settings, and is sold in vial form, pre-filled syringe form, and pre-mixed intravenous bag form. Baxter alone sells approximately 50 million vials of heparin every year. As a commodity pharmaceutical, heparin is relatively inexpensive -- most vials sell for less than one dollar.

The potential side effects of heparin have been well known for decades, and are well documented in the literature and product labeling. These side effects include allergic type reactions.

Heparin, while classified for regulatory purposes as a drug, is in reality a complex biologic, derived from the tissues of living organisms, in this case the intestinal mucosa of pigs. Biologics are by nature more difficult to control and produce in uniform fashion, and demonstrate much more variation in composition than a chemical-based drug.

Baxter produces heparin in "single-dose" vials, which can be used only once, and in "multi-dose" vials, which can be used either to draw individual doses for multiple patients or used to create larger "bolus" doses of heparin for a single patient. Baxter also sells HEP-LOCK, which is used to flush intravenous lines and is much more dilute than therapeutic heparin. Nearly all reported adverse reactions that Baxter has associated with its recent recall have occurred with our multi-dose vials. Baxter has received some reports of allergic type reactions with our higher dose single-dose vials when single doses were combined to create a larger "bolus" dose. Baxter's single-dose vials, multi-dose vials and HEP-LOCK vials are filled using the same active pharmaceutical ingredient ("API").

Your Question Re: FDA Approval

Your February 21, 2008 letter asked, "*Was your firm misled by FDA into believing that the Chinese firm was an approved supplier of an active ingredient of heparin?*" In February 2004, Baxter submitted a NDA Prior Approval Supplement ("PAS") for use of the Scientific Protein Laboratories, L.L.C.'s ("SPL") facility in Changzhou, China ("SPL-CZ") as an alternate supplier for heparin API. Baxter's NDA PAS referenced the Drug Master File ("DMF") that SPL had submitted to the FDA for the SPL-CZ facility. The DMF contains proprietary information accessible to the FDA, but not Baxter, regarding SPL's manufacturing process. The FDA approved the PAS in June 2004. (Please see TAB A.) Baxter was not privy to and would be unable to comment on the FDA's internal process for issuing this approval.

Baxter

Update on Recall

At the end of December 2007, as part of Baxter's normal pharmacovigilance process, Baxter noticed an increase in the rate of allergic-type reactions associated with our 1,000 unit/mL 10 mL and 30 mL multi-dose heparin products. (Please refer to TAB B for a timeline of events). The initial reports came from a few dialysis centers. In response to these initial reports, Baxter's quality specialists analyzed the manufacturing and quality control records for the heparin lots associated with the adverse events. Quality records showed these lots had met all applicable specifications. Baxter also reviewed manufacturing change controls from January – December 2007, and found no changes to product, process or specifications that could have contributed to these events. Further, all raw materials (actives and excipients) used to manufacture these lots conformed to specifications.

Baxter initiated a manufacturing investigation to determine the most probable cause, and on January 9, 2008, Baxter placed inventory for both the 1,000 unit/mL 10 mL and 30 mL product on hold. On January 8, 2008, Baxter's pharmacovigilance group also began visiting sites where adverse events were reported. On January 11, 2008, Baxter contacted the FDA about these increased adverse drug experience reports at some dialysis centers. The reports all concerned patients that experienced one or more of the following events after administration of a loading dose of heparin for hemodialysis: hypotension, flushing, lips tingling, abdominal pain, chest burning, feeling warm, feeling strange, fainting, diaphoresis, shortness of breath, thirst and nausea. Baxter also told the FDA that an investigation had been initiated to determine the most probable cause.

After January 11th, Baxter received additional complaints against additional lots of Baxter 1,000 unit/mL 10 mL and 30 mL multi-dose heparin. On January 14, 2008 Baxter suspended the manufacturing of its 1,000 unit/mL multi-dose products pending the outcome of an internal investigation. Baxter communicated this additional information to the FDA on January 16, 2008, and also informed the FDA that Baxter was initiating a voluntary recall. On January 17, 2008, Baxter issued a voluntary recall of nine lots of Baxter's 1,000 unit/mL multi-dose product.

After this recall was announced, Baxter saw a slight increase in reactions on other lots and sizes of heparin sodium injection beyond the 1,000 unit/mL multi-dose vials that had been recalled. On February 6, 2008 we contacted the FDA to report we were contemplating an expanded recall on the multi-dose vials. On February 8, 2008, Baxter reported to the FDA that there had been 348 unique adverse reaction case reports, with 94% of the reports against the 1,000 unit/mL multi-dose vials, 4% of the reports against the 5,000 unit/mL and 10,000 unit/mL multi-dose vials, and 2% of the reports against the 5,000 unit/mL single dose vial (8 total). Three of these eight single dose reports concerned reports of hypotension during surgery where multiple single dose vials were used to create a large bolus dose.

Baxter

Baxter confirmed with the FDA its intent to recall all multi-dose vials in the marketplace on February 8, 2008. However, since Baxter supplies approximately half of the multi-dose vials of heparin used in the United States, the FDA and Baxter were concerned about the supply of heparin in the market if the recall was expanded. After careful consideration, on February 8th, FDA and Baxter concluded that it was better for public health to allow the Baxter multi-dose vials of heparin to remain in distribution so they could be used with caution in situations where the use of heparin was considered medically necessary and alternate sources of heparin were not available.

This decision was announced to health care professionals on February 11, 2008 in a broadly disseminated Important Safety Information Bulletin. In this safety alert, health care professionals were warned to: balance the clinical need to use these products with the increased potential for experiencing adverse drug reactions; use the lowest dose necessary to achieve the minimum required level of anticoagulation; avoid administering bolus doses if possible; be aware of the increased potential for adverse drug reactions to occur; and be advised to implement measures that allow prompt identification and treatment of the signs or symptoms of adverse reactions. (Please see TAB C.)

On February 19, 2008, there were press reports about APP, the other major supplier of heparin in the US. The press reports indicated that APP had increased production of heparin and that APP had the ability to adequately supply the U.S. market with heparin. Baxter immediately assembled information on its own supply situation, including supply that might become available from non-SPL sources. Baxter initiated a conference call with the FDA on February 22nd and discussed whether it could expand its voluntary recall in light of APP's announcement about their ability to supply the market. The FDA (including the Office of Drug Shortage) wanted some time to examine the issue including market supply of all heparin products. On February 27, 2008, Baxter received final clearance from the FDA that it could recall all of its heparin products from the market. Baxter expanded its recall of this product on February 28, 2008 to include all its multi-dose, single dose and HEP-LOCK products.

Update on Investigations and Findings

Baxter is in the midst of an aggressive "root cause" investigation to understand the underlying reason(s) for the increase in adverse events that it has seen with its heparin product. Its scientists and expert consultants have employed a battery of sophisticated analyses to methodically isolate and rule in or out the multiple variables in the manufacturing process and supply chain.

At this point, Baxter has excluded the manufacturing process elements at Baxter's Cherry Hill, New Jersey manufacturing facility as potential contributors to the root cause. The investigation into the process elements included an analysis of the components that make up the heparin solution and its packaging (the vial, rubber closure, water, sodium chloride and benzyl alcohol), an extensive evaluation of the data collected during manufacture of the products, and a review of the aseptic processing conditions at the time the products were manufactured.

Our investigation report was shared with an investigator from the FDA's New Jersey District Office during the FDA's recent inspection of the Cherry Hill site. That FDA inspection, which started on January 17, 2008, was concluded on February 28, 2008 with no inspectional observations (known as Form 483 observations) issued.

Baxter also tested finished product solutions from "test" and "control" lots. "Control" lots are those where finished product was not showing adverse reactions, while "test" lots were those associated with the cluster of adverse events. Samples from both control and test lots were analyzed, using appropriate analytical methodologies, for the presence of potential leachables and trace elements. The leachables and trace element profiles for the control and test lots were compared, and no meaningful differences were observed.

Approximately three weeks ago, Baxter undertook to use nuclear magnetic resonance (NMR) spectroscopy tests and capillary electrophoresis (CE) tests to identify any differences that might have existed in the chemical composition of the control and test lots. The NMR and CE test results for the test lots showed the presence of extra signals and a peak (respectively, for the NMR and CE tests) that were not present in the API control lots.

Baxter is currently focusing on determining precisely what substance(s) the extra signals/peak represent and what its source might be. Baxter now has an indication that the observed difference may be due to the presence of a heparin-like molecule. We are not certain that the differences observed in the API are the source of the allergic reactions. Since the extra signals and a peak are the only significant difference noted between control and test lots of API, the API is now the focus of Baxter's investigation.

Baxter has since tested samples of API that were processed at SPL's Wisconsin plant, using Chinese-made crude heparin. Baxter's NMR and CE tests found that four out of five of the Wisconsin processed lots that were most recently tested showed the same extra signals/peak that were seen in earlier tests of lots from SPL's China plant. These results suggest that the root cause may be associated with the crude heparin, sourced from China, or from the finishing process resulting in API.

Baxter's Supplier, Scientific Protein Laboratories, Has a 30-Year History of Supplying Heparin API

Baxter's supplier of API is SPL located in Waunakee, Wisconsin. SPL originally supplied API to ESI Lederle, a division of Wyeth that Baxter acquired on December 20, 2002. SPL has supplied Baxter, and previously ESI Lederle, with heparin API for over thirty years. SPL was first listed as an approved supplier of heparin for ESI Lederle in 1972. The only product or service that SPL has ever supplied to Baxter has been heparin sodium API.

SPL initially provided heparin API that was refined from crude heparin made from U.S. porcine intestinal tissue and finished in SPL's facility in Wisconsin. In the 1990's, SPL began to explore sourcing the crude heparin from China. From 1996 to the present, SPL has produced regular shipments of finished heparin API processed at its Wisconsin facility and sourced from Chinese crude heparin material. For an illustration of the heparin supply chain, please see TAB D.

In 1999, SPL created a joint venture with Techpool Bio-Pharma Co., Ltd. called Changzhou-SPL ("SPL-CZ") and later opened a facility for processing crude heparin into API. This facility was inspected by Wyeth's Global Compliance Division for a qualification audit to ensure the facility met all cGMP requirements and the requirements of the business. The SPL-CZ plant successfully completed the qualification audit in 2003.

In February 2004, Baxter submitted a NDA Prior Approval Supplement ("PAS") for use of the Scientific Protein Laboratories, L.L.C.'s ("SPL") facility in Changzhou, China ("SPL-CZ") facility as an alternate supplier for heparin API. Baxter's NDA PAS referenced the Drug Master File ("DMF") that SPL had submitted to the FDA for the SPL-CZ facility. The DMF contains proprietary information accessible to the FDA, but not Baxter, regarding SPL's manufacturing process. The FDA approved the PAS in June 2004. (Please see TAB A.)

As noted above, the first audit of the SPL-CZ facility was the full qualification audit performed by Wyeth Global Compliance in December 2002. (A copy of that audit, and the correspondence after the audit, are included with this letter at TAB E.) In September 2003, Baxter conducted a plant inspection of SPL-CZ. The SPL-CZ facility began to process crude heparin for Baxter in November 2004 and has been continuously supplying finished heparin API product from Chinese sourced crude heparin since that time.

Baxter performed an audit of the SPL-CZ facility on September 20, 2007. This cGMP audit was conducted to verify the effectiveness of the plant's quality systems and technical capabilities. Based on our review of the SPL-CZ facility, Baxter approved SPL-CZ's production of the routine manufacturing of Heparin Sodium UPS, API pending satisfactory responses to the observations included in the report. SPL-CZ produced satisfactory responses on January 19, 2008. Copies of both Baxter's September 2007 audit and SPL-CZ's response to this audit and Baxter's reply are included with this letter. (Please see TAB F.)

Baxter's audit followed the principles of the U.S. Department of Health and Human Services/FDA/CDER/CBER Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients ("Q7A"), an ICH internationally recognized standard. A more comprehensive description of this process is contained in the attached Q7A Good Manufacturing Practice Guidance for API. (Please see TAB G.) The Q7A audit process does not apply to the manufacture of raw materials upstream in the supply chain. Baxter relies upon SPL to effectively monitor and audit SPL's suppliers.

Based on the successful completion of the audits of the SPL-CZ facility and SPL's Wisconsin facility, Baxter can summarize SPL's performance history with Chinese crude heparin prior to current cluster of adverse events as follows:

- Twelve years of successful API manufacturing
- Over 500,000,000 finished doses
- Four FDA inspections/audits
- Five Wyeth/Baxter inspections/audits

A critical part of Baxter's processes for ensuring products meet applicable quality standards is the multiple, rigorous testing done on all lots of incoming API and finished products. For heparin, summaries of this testing, as well as the testing and the supplier quality controls for which SPL is responsible, are shown at TABS H and I. As a matter of course, Baxter performs more than 15 separate tests on the API and finished product as required by applicable compendia, in this case, United States Pharmacopeia (USP) standards. USP is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. Even though SPL meets USP standards and provides its raw materials to Baxter with the USP designation, Baxter re-tests every lot of the API, to ensure that the incoming material meets both USP testing criteria and Baxter's established standards.

Baxter

Baxter's relationship with SPL is governed by a written supply agreement that requires all API produced to conform to all applicable regulatory approvals, cGMP requirements and all applicable rules and regulations, including the FDA Guide to the Inspection of Bulk Pharmaceutical Chemicals. Other than this contractual supply arrangement, Baxter has no other financial or ownership interest in SPL.

Baxter Continues to Investigate All Adverse Event Reports Associated with Heparin, Including Deaths

Baxter monitors drug safety surveillance through its pharmacovigilance (i.e., safety surveillance) group, under the leadership of Dr. Jay Ehrlich, our Senior Director of Safety Operations. The pharmacovigilance group receives, investigates, analyzes and reports on adverse events. All adverse events must be reported to the FDA either on an expedited or periodic basis, regardless of whether there was any causal relationship between the use of the product and the reported event.[1] Accordingly, due care must be taken in characterizing the number and types of adverse events reported to the FDA and the causal association of those events to the drug at issue.

A few weeks ago, it was widely reported in the press that there were four deaths "linked" to Baxter's heparin. Baxter's investigation of these four initial fatality reports is substantially complete. It is unlikely that there is a causal relationship between the allergic reactions involved in the current recall and the four patient fatalities. In one case, investigation revealed that the patient had not received Baxter heparin. Another case, although reported to Baxter recently, actually occurred in early 2005, almost three years before the increase in adverse reactions that triggered the recall. A third case involved a death as a consequence of bowel obstruction and overwhelming infection, with no evidence of causal association with heparin use. The fourth case involved the death of a cardiac patient in which the role of heparin, if any, was as one of several potential causes of thrombosis, a well-documented side-effect of heparin, and one that is not consistent with the types of adverse reactions reported during the cluster that led to the recall.

The fact that these four initial cases are unlikely to be causally related to the recall illustrates the importance of using care in characterizing the association between the use of a drug or biologic therapy (like heparin) and a temporally associated death. Unfortunately, some press reports have used words such as "linked" or "tied," which can create a false impression of a causal relationship when, in fact, the current medical facts do not support a conclusion that the fatal outcome was a result of an allergic reaction.

---

[1] Regulatory requirements and pharmacovigilance practice use the term "related" to classify cases where there is a likely causal relationship between an adverse event and a drug, but also in those cases where a lack of information does not allow for the exclusion of a causal link. In other words, a case may be designed as "related" although there is no data available to actually substantiate a causal relationship between drug and adverse event.

The difficulty of characterizing a causal relationship is exacerbated in the types of patients who require heparin therapy: patients with end-stage renal disease, clotting tendencies, acute heart attacks, blood clots in the legs or lungs, or patients requiring cardiovascular procedures, including open-heart surgeries. In such an ill and complex population of patients, deaths are unfortunately more likely to occur for reasons having nothing to do with heparin therapy. It would be medically incorrect to assume that, simply because heparin was present at or around the time of death, it played a causal role in the death. Similarly, to indiscriminately ascribe a "link" or "tie" to heparin in these circumstances is inappropriate from a public health perspective, given the critical role heparin therapy plays in saving tens of thousands of patient lives each day.

The second issue impacting Baxter's pharmacovigilance effort is the wide publicity associated with this heparin recall, which has triggered a substantial increase in adverse event reports, many of which lack the substantial medical detail required to determine whether a heparin product was actually involved in the report, if that heparin product was a Baxter product, and what causal relationship between the reported adverse events and heparin, if any, exists. Typically, these reports are being provided by a patient or a relative of a patient who has no medical training and no access to information about the drug the patient actually received, the manufacturer of that drug, route of administration or formulation. Baxter's efforts to investigate further have been hampered by the unwillingness of clinicians and hospitals to discuss reports, often at the behest of hospital risk managers concerned with malpractice liability after the mischaracterization of the four patient deaths as "linked" to the recall.

Since December 15, 2007, Baxter has received fourteen reports involving a fatal outcome coincident with or subsequent to the use of a heparin product that has either been confirmed as, or is likely to be, a Baxter heparin product. In eight of these cases, the timing of the heparin administration relative to the patient's death or the current cluster of allergic reactions in combination with the specific medical conditions of each patient, makes it unlikely that these deaths were causally related to the allergic reactions addressed in our recall. In two of the cases, the only information Baxter has is contained either in a lawsuit or the press coverage of that lawsuit; no medical professional or family member has provided any medical records or other credible evidence that allows medical consideration or verification of the allegations regarding the plaintiffs' deaths. In the four remaining cases, each patient had multiple underlying complex medical conditions and three had either undergone, or was in the process of undergoing, invasive cardiac surgery; although each of these patients suffered an allergic-type reaction to heparin that may have contributed to the adverse outcome, there is not yet enough medical data available to draw a firm conclusion. During the same time frame, Baxter estimates that more than 10,000,000 doses of our heparin product were administered. A summary of this adverse event information is included at TAB J.

Baxter will continue to investigate and analyze these reports to assess whether the reported adverse reactions were causally related to the cluster of allergic reactions that are the subject of the recall, and will continue to forward all reports received to FDA within a markedly compressed timeframe of seven days from Baxter's initial awareness.[2]

* * *

I appreciate this opportunity to provide an update on the status of Baxter's investigation into the root cause of the allergic reactions associated with heparin. I have asked my counsel at King & Spalding to be in contact with your staffs to arrange for a discussion of your needs for further documentation or information. In the meantime, I will continue to keep the Committee updated on the progress of our investigation into the root cause of these allergic reactions.

Sincerely,
Baxter Healthcare Corporation

Peter J. Arduini
Corporate Vice President
President, Medication Delivery

---

[2] The usual reporting timeframe per FDA regulations ranges from 15 days to as long as months or years, depending on the seriousness of the adverse event and whether or not it is reflected in the approved product labeling.

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

ONE HUNDRED TENTH CONGRESS
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

February 21, 2008

The Honorable Michael O. Leavitt
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Leavitt:

We have attached our letter to Food and Drug Commissioner von Eschenbach regarding an alleged policy change that may place Americans in the same grave danger currently faced by consumers of Baxter's blood-thinning drug Heparin. In addition to the letter's request for policy clarification and staff interviews, the Committee on Energy and Commerce needs additional information to determine if emergency legislation is needed to protect Americans from prescription medications that have been insufficiently investigated prior to approval.

As the Administration's official responsible for both the Food and Drug Administration (FDA) and the Office of General Counsel (OGC), we request that you supply the Committee with all records in your possession or control relating to FDA's preapproval inspection policy. These records should include, but are not limited to, any and all legal memoranda, training manuals, policy statements, budget justification documents, and briefing materials. The terms "records" and "relating to" are defined in the attachment to this letter.

In addition, we request that you explain to the Committee your interpretation of the legal status of drugs shipped into United States commerce by a drug company that knew or should have known that FDA had not performed a preapproval inspection, as is alleged in the Heparin case.

Please provide the requested information by no later the close of business on Friday, February 22, 2008, as the Committee needs reasonable time to prepare for your upcoming testimony. Should you have any questions regarding this request, please contact David Nelson or Chris Knauer of the Committee staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

ONE HUNDRED TENTH CONGRESS
U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

March 12, 2008

Mr. David Strunce
Chief Executive Officer
Scientific Protein Laboratories, LLC
700 East Main Street
Waunakee, WI 53597–0158

Dear Mr. Strunce:

Under Rules X and XI of the Rules of the United States House of Representatives, the Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations are investigating the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with prescription drugs. As part of this investigation, we are looking into the February 28, 2008, recall of heparin by Baxter International, Inc.

We understand that Baxter International, Inc. purchased the active ingredient for their recalled heparin products from Scientific Protein Laboratories, LLC and that the raw heparin ingredients, at least in substantial part, were manufactured in China. We are concerned that the regulatory framework to protect American patients from the ill effects of contaminated pharmaceutical products may be ineffective.

Therefore, we ask that you provide the following:

1. The names, addresses, principal officers, and contact information for all suppliers of raw heparin products to Scientific Protein Laboratories, LLC since 2002;

2. All FDA Establishment Inspection Reports (EIRs) and form 483s related to Scientific Protein Laboratories, LLC and any supplier of raw heparin products since 2002;

3. All FDA warning letters related to Scientific Protein Laboratories, LLC and any supplier of raw heparin products since 2002;

Despite many red flags, BP executives issued a "budget challenge" in late 2004 to cut spending at Texas City by 25 percent. Despite pleas for adequate funding from the Texas City refinery manager, BP was unwilling to reinstate full funding.

BP's process safety problems were not confined to Texas City. BP commissioned former Secretary of State James Baker to lead an assessment of safety at BP's U.S. refineries. The January 16, 2007, report concluded, "significant process safety issues exist at all five U.S. refineries, not just Texas City." OSHA assessed BP a $2.4 million fine for 32 "willful" violations at its Toledo, Ohio, refinery in 2006. In announcing this penalty, the Administrator of OSHA said, "It is extremely disappointing that BP Products failed to learn from the lessons of Texas City to assure their workers' safety and health."

At the same time BP executives were cutting funds for safety at Texas City, they were cutting safety costs at the Prudhoe Bay, Alaska, oil field. On March 2, 2006, approximately 201,000 gallons of crude oil were found leaking from an oil transit line in Prudhoe Bay. What started as a single spill ended in the discovery of widespread corrosion in BP's pipelines, and the temporary shutdown of the Prudhoe Bay oil field. This caused oil and gasoline prices to skyrocket due to the loss of 8 percent of U.S. oil production. This shutdown occurred because BP allowed its oil transit lines to become unserviceable.

The Committee on Energy and Commerce obtained internal BP e-mails showing that BP's executives had issued "budget challenges" and directed "top down cost cutting" in Alaska without regard to the safety of its oil pipelines. BP's own consultant, Booz Allen, found that "budgeting was largely driven by top down targets" rather than based on an analysis of risks, and "top down targets were considered sacrosanct and rarely exceeded."

The "McNulty Memorandum" on Federal Prosecution of Business Organizations states, "Only rarely should provable individual culpability not be pursued, even in the face of an offer of a corporate guilty plea..."

BP Product's ability to comply with the terms of this plea agreement is dependent upon funds from its parent, BP Plc, and its Board of Directors. The Government, however, charged a fourth-tier subsidiary, even though it cannot make budgeting decisions related to process safety.

In its January 22, 2008, brief in support of this plea agreement, BP stridently defends the legal protections it created through a multi-layered corporate structure that immunized the corporate parent and points to 35 other plea agreements that exclude the parent company. BP asserts:

> "[I]t is a standard provision for a corporate plea agreement. The reason for the provision is obvious—a corporation has no reason to plead guilty when its parent or subsidiary corporations could be potentially charged for the same conduct."

Please respond to the following questions regarding this plea agreement:

1. Did DOJ intentionally exclude the parent company from this plea agreement? Is this exclusion consistent with DOJ policy? Please explain the basis for failing to pierce BP's corporate veil.
2. Did DOJ or the Environmental Protection Agency (EPA) investigate the role of the parent company, BP Plc, in connection with repeated cost-cutting decisions given its knowledge that there were degraded safety conditions at this refinery?
3. Has DOJ or EPA investigated whether there was potential culpability by individual BP executives and managers in connection with cost cutting and their knowledge of degraded safety conditions at this refinery for more than seven years? Has this investigation been concluded?
4. Did OSHA or EPA make any criminal referrals to DOJ for individual BP executives or managers?
5. Has DOJ provided EPA with the necessary legal resources to investigate BP executives in the U.S. and United Kingdom?

II. By sidestepping the corporate parent in favor of charging a fourth-tier subsidiary, did the Justice Department consider the totality of BP's corporate misconduct when assessing "the history and characteristics of the defendant" as part of the criminal penalty process under 18 U.S.C. 3553?

BP's near-term history contains dozens of civil and criminal violations. The documents filed with the District Court, however, only mention two violations involving BP in Alaska.

1. Were environmental and safety violations at the refineries in Ohio, Indiana, and California not relevant? Were price fixing, pipeline safety, and oil royalty violations not relevant?
2. Did DOJ review the history and characteristics of all BP corporate affiliates operating in the U.S. when evaluating BP's history of civil and criminal violations? Was a comprehensive review provided to the Court by the U.S. Attorney?
3. If this information was not provided to the Court, did DOJ fail to pierce the corporate veil with respect to BP's history of violations—both civil and criminal?

"consulting with crime victims prior to reaching a plea agreement would be impracticable" and that any "suggestion of an admission of criminal responsibility by BP Products prior to the actual signing of a plea agreement would prejudice BP Products."

This is at odds with the Attorney General's *Guidelines for Victim and Witness Assistance* which states, "Responsible officials should make reasonable efforts to notify identified victims of, and consider victim views about, any proposed or contemplated plea negotiations."

The U.S. Attorney did not have to choose between conducting secret plea negotiations and protecting crime victim rights. The victims' rights to confer were blocked until *after* the deal was finalized, and DOJ made its public announcement on October 25, 2007. It is curious that, at precisely the time DOJ was negotiating with BP on finalizing this plea agreement and arranging for a nationwide press conference to announce two other plea agreements involving BP's criminal conduct, the U.S. Attorney argued in an *ex parte* communication with the Court that it was impractical to notify victims and consult their views.

Did DOJ public relations considerations trump substantive consultations with victims? Having been locked out of the process when consultations might have been meaningful, the victims now face a joint defense by DOJ and BP to fight off any challenge to the adequacy of this plea agreement.

1. Did DOJ honor the Attorney General's *Guidelines for Victim and Witness Assistance* by consulting with the victims (or their representatives) about plea negotiations before the agreement was reached?
2. In the past two years, please identify all criminal plea agreements where DOJ sought court permission to avoid providing notice or avoid consulting with clearly identifiable victims (e.g., identifiable by having brought a civil suit) about the contents of a plea agreement before the plea agreement was reached.
3. Please provide the factual basis that supports the U.S. Attorney's contention that it would have been impractical to notify the Texas City refinery victims in advance of a plea agreement and provide opportunity for input. What alternatives had DOJ considered and rejected? In a February 21, 2008, opinion, Judge Lee Rosenthal raised this same question.
4. Between October 18 and 25, 2007, when the U.S. Attorney told the Court that he could not consult with the victims because it was impracticable, is it true that DOJ was making arrangements to consolidate the announcement of three criminal matters involving BP at a Washington, D.C. press conference? To what extent did preparations for a major announcement preclude discussions with victims during plea negotiations?

Please provide answers to the questions outlined above within 10 days of receipt of this letter. In addition, please provide:

1. All documents, communications, spreadsheets, memoranda, or e-mails prepared by DOJ or EPA that estimate BP's pecuniary benefits enjoyed as a result of its noncompliance at Texas City.
2. All communications between or within the Office of the U.S. Attorney, Main Justice, or BP (or its counsel), including e-mails, memoranda, or letters that assess, evaluate, or discuss whether to notify victims prior to the conclusion of plea negotiations with BP.
3. All communications, including memoranda, e-mails, or letters within or between the Office of the U.S. Attorney or Main Justice and attorneys for BP Products regarding the possibility of consolidating the press announcement of deferred prosecution agreement involving the BP propane price fixing case, the BP Alaska misdemeanor plea, and the Texas City felony plea.

Please note that the Committee does not expect the production of documents, if any, which were prepared for a grand jury.

Finally, we respectfully request that you personally assess whether this plea agreement with BP has inherent weaknesses that leave both workers and the public inadequately protected, whether there is individual culpability, and whether DOJ has struck a deal that, given BP's long history of noncompliance, will be an ineffectual deterrent to future violations.

We also request that you brief the Committee on these issues. Please contact us or have your staff contact John F. Sopko or Richard Miller with Committee staff at (202) 226-2424 to arrange for a time to meet and discuss these matters in detail.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
EDWARD J. MARKEY, MASSACHUSETTS
RICK BOUCHER, VIRGINIA
EDOLPHUS TOWNS, NEW YORK
FRANK PALLONE, Jr., NEW JERSEY
BART GORDON, TENNESSEE
BOBBY L. RUSH, ILLINOIS
ANNA G. ESHOO, CALIFORNIA
BART STUPAK, MICHIGAN
ELIOT L. ENGEL, NEW YORK
ALBERT R. WYNN, MARYLAND
GENE GREEN, TEXAS
DIANA DeGETTE, COLORADO
VICE CHAIRMAN
LOIS CAPPS, CALIFORNIA
MIKE DOYLE, PENNSYLVANIA
JANE HARMAN, CALIFORNIA
TOM ALLEN, MAINE
JAN SCHAKOWSKY, ILLINOIS
HILDA L. SOLIS, CALIFORNIA
CHARLES A. GONZALEZ, TEXAS
JAY INSLEE, WASHINGTON
TAMMY BALDWIN, WISCONSIN
MIKE ROSS, ARKANSAS
DARLENE HOOLEY, OREGON
ANTHONY D. WEINER, NEW YORK
JIM MATHESON, UTAH
G.K. BUTTERFIELD, NORTH CAROLINA
CHARLIE MELANCON, LOUISIANA
JOHN BARROW, GEORGIA
BARON P. HILL, INDIANA

DENNIS B. FITZGIBBONS, CHIEF OF STAFF
GREGG A. ROTHSCHILD, CHIEF COUNSEL

JOE BARTON, TEXAS
RANKING MEMBER
RALPH M. HALL, TEXAS
FRED UPTON, MICHIGAN
CLIFF STEARNS, FLORIDA
NATHAN DEAL, GEORGIA
ED WHITFIELD, KENTUCKY
BARBARA CUBIN, WYOMING
JOHN SHIMKUS, ILLINOIS
HEATHER WILSON, NEW MEXICO
JOHN B. SHADEGG, ARIZONA
CHARLES W. "CHIP" PICKERING, MISSISSIPPI
VITO FOSSELLA, NEW YORK
ROY BLUNT, MISSOURI
STEVE BUYER, INDIANA
GEORGE RADANOVICH, CALIFORNIA
JOSEPH R. PITTS, PENNSYLVANIA
MARY BONO MACK, CALIFORNIA
GREG WALDEN, OREGON
LEE TERRY, NEBRASKA
MIKE FERGUSON, NEW JERSEY
MIKE ROGERS, MICHIGAN
SUE MYRICK, NORTH CAROLINA
JOHN SULLIVAN, OKLAHOMA
TIM MURPHY, PENNSYLVANIA
MICHAEL C. BURGESS, TEXAS
MARSHA BLACKBURN, TENNESSEE

March 19, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

The circumstances surrounding the outbreak of adverse reactions associated with heparin raise questions about the Food and Drug Administration's (FDA) current ability to assure the safety of foreign drugs or pharmaceutical ingredients imported for use in the U.S. drug supply. In particular, the Committee on Energy and Commerce's investigation into why FDA mistakenly identified the wrong Chinese facility as the supplier of bulk heparin for Baxter Laboratories has revealed questionable policies and practices concerning FDA's assessment and inspection of drug manufacturing risks among foreign firms, especially, in this instance, within China.

FDA stated in response to the February 21, 2008, letter from Chairman Dingell and Subcommittee Chairman Stupak that its policy has been, and continues to be, to approve drugs after verifying that a drug's manufacture, processing, and packing are adequate to preserve the drug's identity, strength, quality, and purity. Verification that these standards are met is based upon a recent inspection of the manufacturing facility or facilities named in a new drug or abbreviated new drug application. FDA noted further that, if it had a "recent, satisfactory inspection on record for a given facility named in the application, we generally will not conduct a new pre-approval inspection of that facility…" unless FDA determines "…the circumstances warrant it."

In the course of investigating the heparin case, we have learned that FDA essentially relies upon a vague and ad hoc policy when deciding whether "the circumstances warrant" a preapproval inspection. In interviews with Majority and Minority Committee staff, officials with the Center for Drug Evaluation and Research (CDER) initially maintained that the Chinese supplier of the bulk heparin product was not inspected as a direct result of mistaken identity with a manufacturer of a similar name. When seeking to understand how this mistake was made, however, we discovered a larger and broader problem—FDA's decision to waive the inspection was not based solely on mistaken identity, but also on questionable judgment regarding when to conduct preapproval inspections.

According to FDA's approach in this heparin case, a Chinese plant previously inspected for making a diuretic and antibiotic for export to the United States would not need a new inspection for initiating a completely different line of product, a biological line, for export. Committee staff was provided no clear rationale or policy guidance for making this decision. It remains unclear whether FDA has any rational policy for deciding when the manufacturing process for one drug is sufficient to assure the quality of the process for an additional different drug to be made in that same facility.

Indeed, of the 10 criteria in the CDER preapproval policy regarding whether a plant could be determined to be in compliance without a new physical inspection, neither facility location, complexity of the manufacturing process, nor sensitivity of the final drug product make the list. While the formal policy document dealing with preapproval inspections does not say so explicitly, the CDER compliance official responsible for the decision not to inspect the plant in China told the Committee staff that neither the complexity of the heparin extraction process nor the location of the plant in China would compel him to order a preapproval inspection.

This policy—or lack thereof—is even more troubling because FDA has not been able to assure us that all Chinese facilities providing product to the U.S. drug market have ever received a single preapproval inspection, let alone follow-up surveillance inspections necessary to assure continued quality and safety. Both the Committee's own investigation and the U.S. Government Accountability Office's (GAO) audit have found that for China alone—now one of the largest producers of drug product for the U.S. market—FDA has only been able to inspect between 10 and 20 firms each year against a backlogged inventory of more than 700 firms (which are only growing in number). At this inspection rate, FDA can only inspect a Chinese firm exporting drug products to the U.S. once every 40 to 50 years.

The policy for choosing follow-up surveillance inspections of foreign plants also generally appears ad hoc and based on vague criteria. For example, it is not clear why certain foreign firms are selected for a follow-up surveillance inspection or what drives the duration FDA allows between such inspections. While FDA has repeatedly told staff that these decisions are based on a sophisticated "risk-based model," a GAO audit of this program suggests FDA's model is limited in value because it is predicated on poor or incomplete data. As noted by GAO in November 1, 2007, testimony before the Subcommittee on Oversight and Investigations, "FDA lacks sufficient data to make an accurate assessment of the potential risk of [foreign drug-making] establishments." In other words, any model based on limited data necessarily has limited capability in predicting risk.

In light of this situation, we seek additional information to evaluate FDA's current practices and policies with regard to its risk assessment of drug product from China. Accordingly, pursuant to our ongoing investigation of the ability of FDA to ensure the safety of the Nation's drug supply, we formally repeat a long-standing request from the Committee for a listing of each of the more than 700 plants operating in China that are registered to export to the United States, what they manufacture, and their inspection histories. Alternatively, you may supply the most recent Form 483 report of inspection for each facility. Further, for each Chinese plant, please provide a list of each manufacturer of finished drug products that has been authorized by FDA to import active pharmaceutical ingredients (APIs) or other raw material ingredients from these Chinese suppliers. Please supply these records along with inspection histories for each of these firms since January 1, 2001, within two weeks of the receipt of this request.

In addition, FDA has previously requested and received from China reports of China's own inspections of Chinese pharmaceutical firms. Therefore, we request that, if not already done so, you obtain the most current report of pharmaceutical drug firms from China's State Food and Drug Administration that have been identified through China's own inspections as producing counterfeit products or products not meeting Chinese standards, and provide this information to us.

With regard to the heparin case, we are aware of the intense efforts of FDA to isolate the source of the contamination and determine how it reached American consumers. We have avoided any formal hearing pending FDA's determinations. Given FDA policies, however, leading to CDER's failure in the heparin matter and the continued inability of FDA to ensure the quality of drug imports, a public discussion of the policy and resource issues related to heparin is needed.

Accordingly, please note that the Subcommittee on Oversight and Investigations intends to hold a hearing on April 15, 2008, on this matter. We expect that you will provide the Committee staff with all documents requested that are related to the FDA approvals for the manufacture and sale of heparin and for the plant that was confused with the Scientific Protein Laboratories (SPL) application. Those records should be provided forthwith.

If you have any questions regarding these requests, please have your staff contact Chris Knauer or David Nelson of the Majority Committee staff at (202) 226-2424 or Peter Spencer of the Minority Committee staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton

Joe Barton
Ranking Member

Bart Stupak

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

John Shimkus
Ranking Member
Subcommittee on Oversight and Investigations

From: Mason, Stephen [mailto:Stephen.Mason@fda.hhs.gov]
Sent: Wednesday, March 05, 2008 6:30 PM
To: Knauer, Chris; Nelson, David; Slobodin, Alan; Spencer, Peter; Schloegel, Scott P
Cc: Dorsey, David (HELP Committee); Lyons, Matthew; Prince, Diane; Meister, Karen G
Subject: Follow up questions

Gentlemen,

Here are some of the answers and documents that have been previously requested. We continue to work on responding to all, as well as confirming a briefing time for the next meeting.

What is the name of the facility that was mistaken for SPL in the EES database?
Changzhou Pharmaceutical Factory No. 1

What products do they manufacture? They manufacture Hydrocholorothiazide and Doxycycline hyclate.

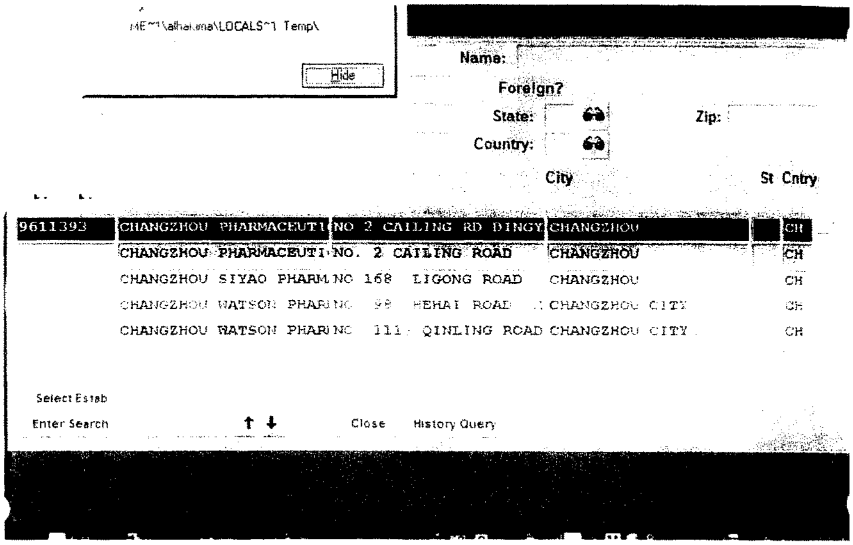
When were they inspected? The facility was last inspected in October 2005. They were also inspected in January 1997, January 1999, and October 2002.

Please provide the EES database screen shot.

Attached is the screen shot. Please note (as we mentioned in the briefing) that there is not a way to recreate what firms were present on the search at the time the error occurred.

Please provide the compliance guidance used to make pre-approval inspection determinations.

This is also attached.



Name:

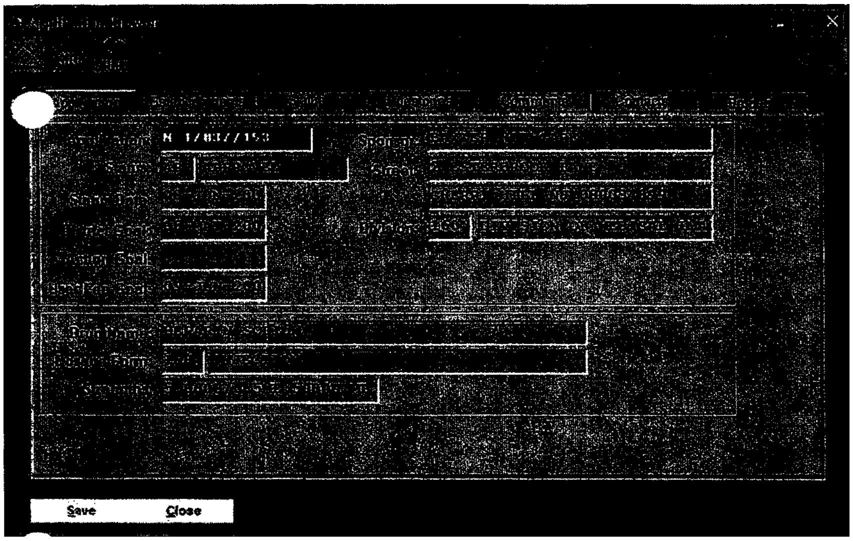
Foreign?

State:

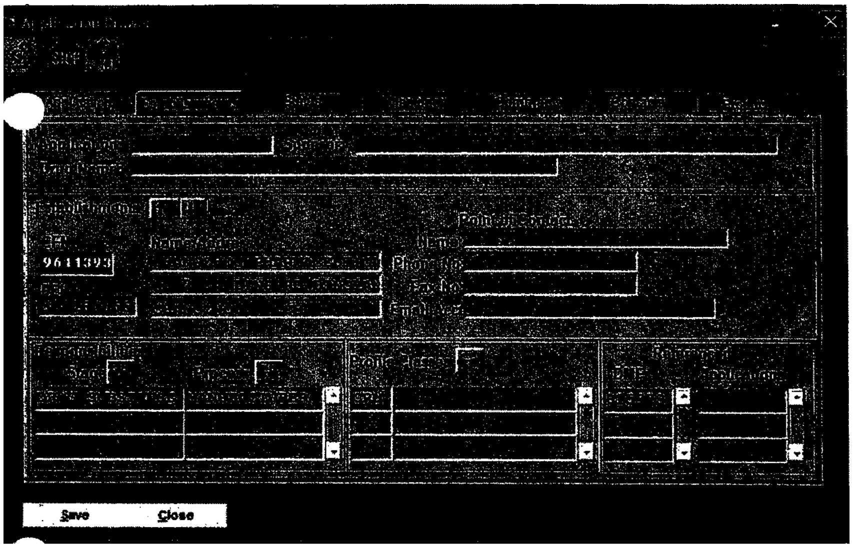
Zip:

Country:

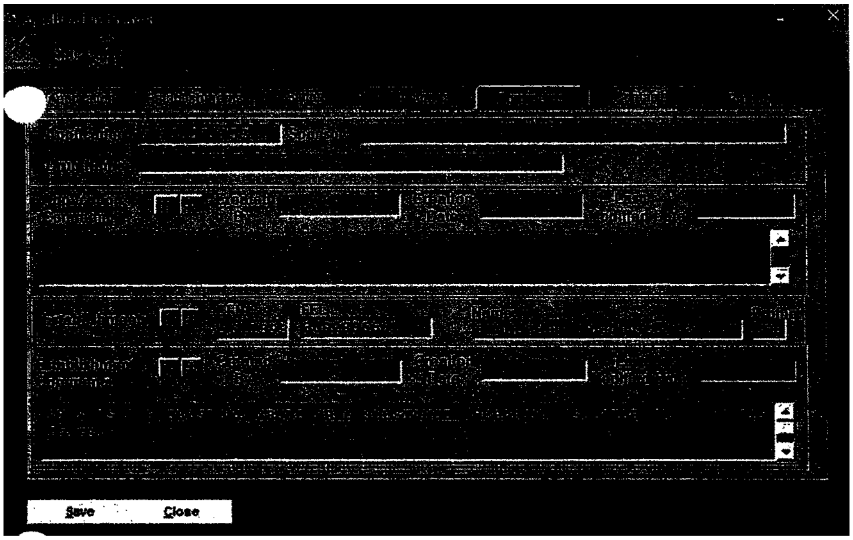
			City	St	Cntry
9611393	CHANGZHOU PHARMACEUTI	NO 2 CAILING RD DINGY	CHANGZHOU		CH
	CHANGZHOU PHARMACEUTI	NO. 2 CAILING ROAD	CHANGZHOU		CH
	CHANGZHOU SIYAO PHARM	NO 168 LIGONG ROAD	CHANGZHOU		CH
	CHANGZHOU WATSON PHAR	NO 98 HEHAI ROAD	CHANGZHOU CITY		CH
	CHANGZHOU WATSON PHAR	NO 111 QINLING ROAD	CHANGZHOU CITY		CH

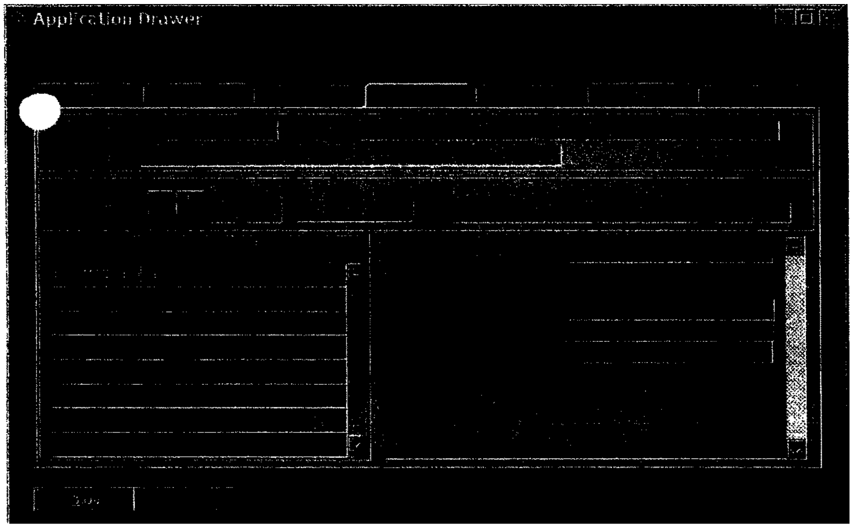


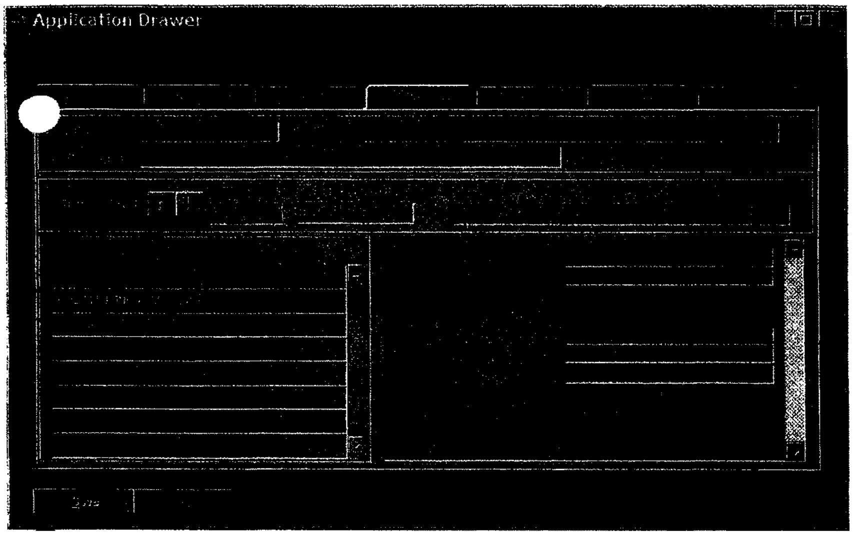
N 17/837/153

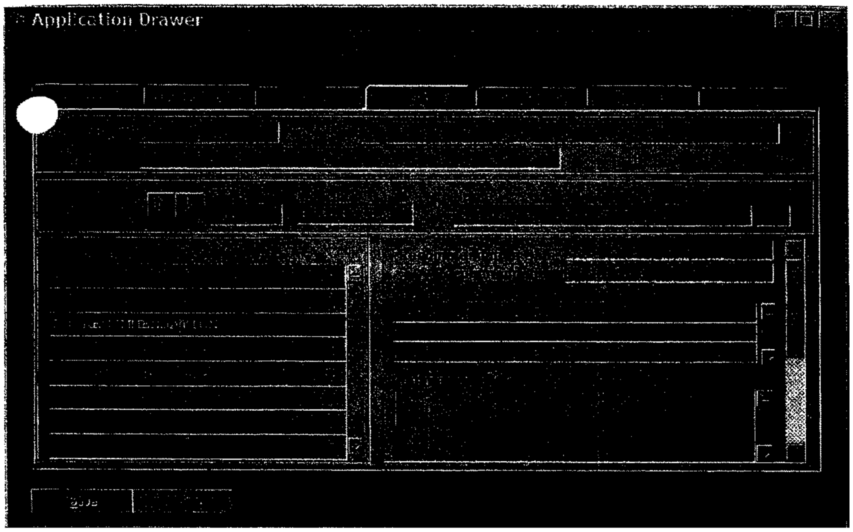


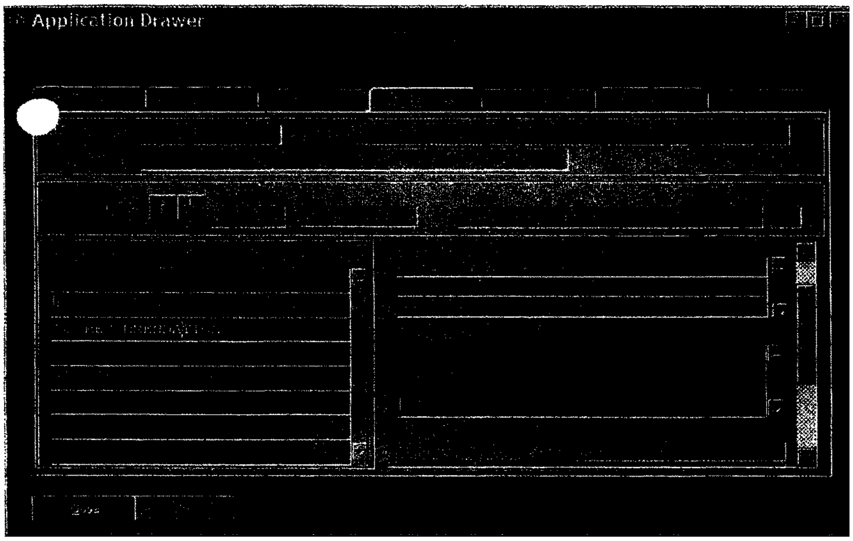
9611393

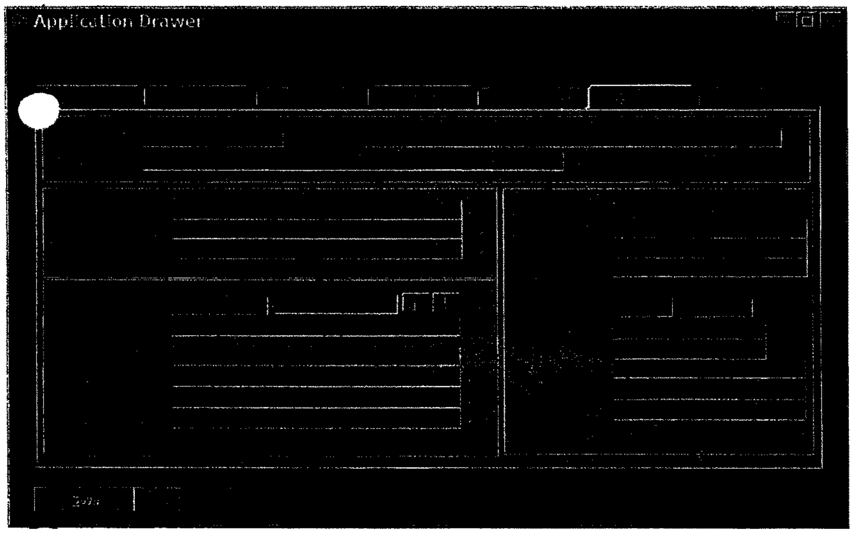

Save
Close

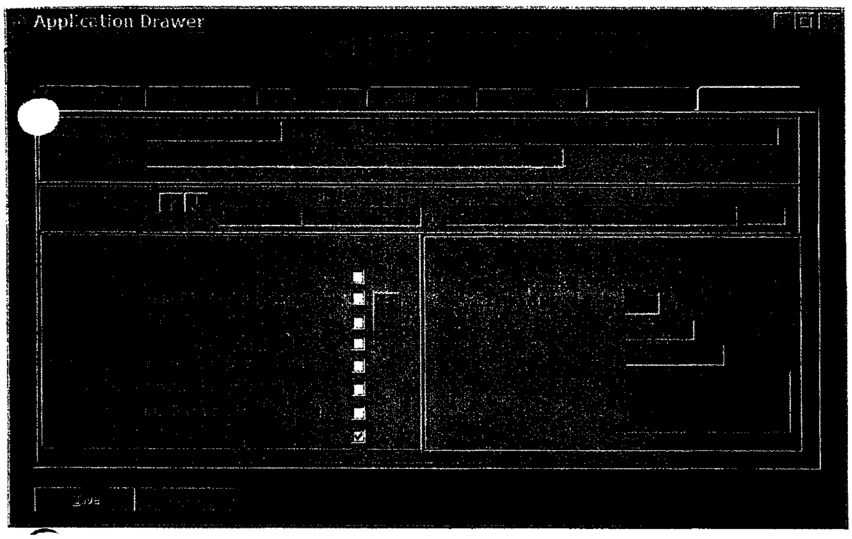

Application Drawer

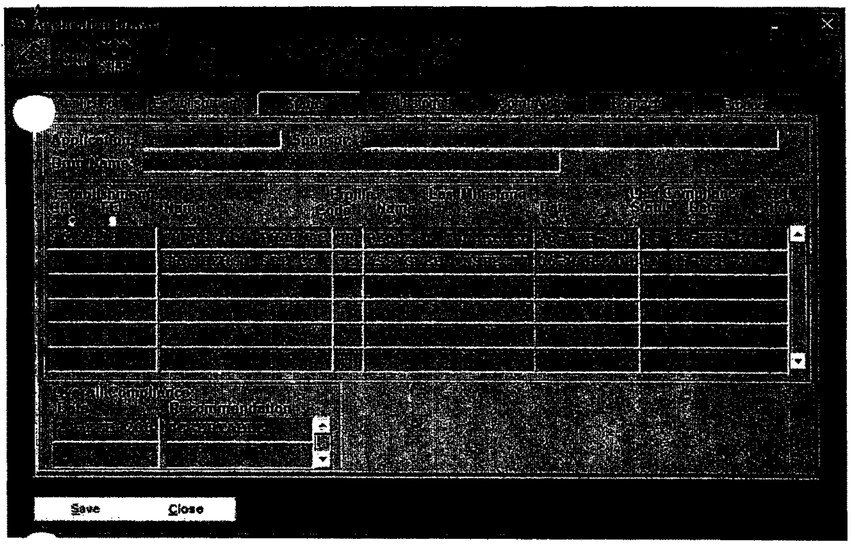

Application Drawer


Application Drawer


Application Drawer


Application Drawer


Application Drawer
Save


Application:
Sponsor:
Brand Name:
Establishment
Name
Profile Code
Name
Date
Status
Overall Compliance
Date
Recommendation
Save
Close

Agency management has determined that the CDER application review process, and the Districts' CGMP inspection and application data audit activities, can be coordinated to improve the efficiency of the preapproval process by encouraging CDER application reviewers, and District investigators and analysts to consult with each other in the course of carrying out their mutual responsibilities.

Accordingly, District investigators and analysts who have questions to discuss with CDER scientists assigned to applications should call the individual whose name appears on the District assignment, or when the CDER reviewer is unknown, to call the appropriate CDER contact who will locate the individual(s) assigned to the application(s) in question and arrange for them to return the call. Similarly, CDER application reviewers who wish to communicate with investigators and analysts performing inspections and laboratory investigations related to the application they have under review will call the preapproval program contact in the appropriate District for assistance in locating the assigned District investigator(s)/analyst(s). (See Part VI for a list of CDER and District program contacts.)

STRATEGY FOR ASSIGNING INSPECTIONS

The strategy for assigning inspection requests for preapproval inspections has been divided into two categories, (1) categories that will regularly prompt an inspection request, and (2) categories when the district office may elect to perform an inspection.

A. *The following categories will regularly prompt a preapproval or CGMP inspection request from CDER Office of Compliance. It is anticipated that the inspections will be conducted except when ORA Field offices recommend the inspection need not be completed:*

   1. *New molecular entities (NMEs) (includes finished drug product and the active pharmaceutical ingredient)*
   2. *Priority NDAs*
   3. *First application filed by an applicant*
   4. *For-Cause inspection*
   5. *For original applications, if the current CGMP status is unacceptable or greater than 2 years*
   6. *For certain pre-approval supplements, such as site change or major construction, if the CGMP status is unacceptable*

7. *Treatment IND inspections*
8. *Information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients*

B. *The district office will have the opportunity to determine if a preapproval inspection is warranted for the following categories. ORA will be queried on the need to conduct a preapproval inspection via the "10 day status" request process in EES.*

1. *All original applications not listed above*
2. *All preapproval supplements not listed above*

C. *Currently, CDER will request a 10-day status report for CBE supplements. Districts should use their knowledge of the firm to assess the need for a prompt inspection of the facility. Districts may also, at their discretion, assign and conduct inspectional audits above and beyond those for which they receive specific headquarters assignment.*

Autor, Deborah

From: Horowitz, David
nt: Monday, March 31, 2003 6:53 AM
: Temple, Robert; Jenkins, John K
Cc: Allen, Susan S; Famulare, Joseph; Autor, Deborah; Axelrad, Jane A
Subject: Fw: Inspections of "Immediate Public Health Impact"

FYI, re OCC's opinion on approvals without preapproval inspections.

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

-----Original Message-----
From: Wion, Ann <AWion@OC.FDA.GOV>
To: Horowitz, David <HorowitzD@cder.fda.gov>
CC: Axelrad, Jane A <AXELRADJ@cder.fda.gov>; Whipkey, Lynn <LWhipkey@OC.FDA.GOV>; Ray, Seth <SRay@OC.FDA.GOV>; Troy, Daniel <DTroy@OC.FDA.GOV>
Sent: Sun Mar 30 23:09:18 2003
Subject: RE: Inspections of "Immediate Public Health Impact"

This looks fine. I would emphasize that if FDA has found the GMP's inadequate to preserve the product's identity, strength, quality, and purity, under 505(d)(3), FDA is to refuse to approve the application. (See also 21 CFR 314.105(a) and (c) and 314.125(b)) In other words, I agree with you that in such a case FDA would be accountable for failing meet the statutory standard for approval; this could include tort liability for the government.

Thanks.

-----Original Message-----
From: Horowitz, David
Sent: Wednesday, March 26, 2003 7:19 PM
To: Wion, Ann
Cc: Axelrad, Jane A
Subject: FW: Inspections of "Immediate Public Health Impact"

Anne:

Please let us know if you have any concerns with this approach. Thanks.

David

David J. Horowitz, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
301-827-8910 (voice)
301-827-8901 (fax)

---Original Message-----
From: Jenkins, John K

Sent: Wednesday, March 26, 2003 7:04 PM
To: Albrecht, Renata; Barnes, Sandy L (CDER); Birnkrant, Debra B;
Chambers, Wiley A; Chowdhury, Badrul A; Collier, Bronwyn E; DeBellas,
Carmen; DeCicco, Anthony W; Dubeau, Julieann; Frank, Ellen C; Galliers,
id M; Ganley, Charles J; Gavrilovich, Lillian; Goldkind, Lawrence;
iebel, Donna J; Hilfiker, David R; Jani, Parinda; Johnson, Kati;
Justice, Robert; Kang, Kyong A; Katz, Russell G; Kober, Margaret;
Korvick, Joyce A; Kozma-Fornaro, Mary J; Laughren, Thomas P; LeSane, F
V; Locicero, Colleen L; Loewke, Sally A; Love, Patricia Y; Mann,
Marianne C; McDonald, Zelda M; Murray, Jeffrey S; Nighswander, Robbin M;
Orloff, David G; Parks, Mary H; Pazdur, Richard; Pease, Dorothy W;
Rappaport, Bob A; Ripper, Leah W; Roeder, David L; Rumble, Terri F;
Shames, Daniel A; Simon, Lee; Soreth, Janice M; Stockbridge, Norman L;
Throckmorton, Douglas C; Wilkin, Jonathan K; Williams, Grant A; Behrman,
Rachel E; Beitz, Julie G; Bull, Jonca; Goldberger, Mark J; Houn,
Florence; Kweder, Sandra L; Meyer, Robert J; Temple, Robert
Cc: Colangelo, Kim M; Cross, James; Kweder, Sandra L; Jenkins, John
K; Horowitz, David; Axelrad, Jane A; Famulare, Joseph; Temple, Robert;
Allen, Susan S
Subject: FW: Inspections of "Immediate Public Health Impact"

Folks

Given the current ban on all international travel other than "essential" travel as defined in Dr. McClellan's e-mail earlier this week, I had asked David Horowitz for an update on how the field and compliance were handling foreign inspections and how this may impact on our PDUFA goal dates and approval decisions. Joe Famulare's e-mail that I forwarded to earlier answered part of the question; i.e., compliance and the eld are currently only proceeding with foreign inspections for priority drugs (unless we tell them that another drug that is not a priority review also meets the "mission critical" part of the essential definition). Attached below is a further answer from David Horowitz to help clarify some of our options with regard to approving an important product without the result of a pre-approval inspection and our ability to send a "complete" response letter (i.e., an AE or NA letter) that lists the lack of a pre-approval inspection as a deficiency and meet our PDUFA goal dates.

I would offer the following guidance from OND IO:

1. If you have a pending application for an important product that is otherwise ready for approval with the exception of the foreign pre-approval inspection (i.e., no other deficiencies that could not be easily worked out to allow for an approval), please discuss this issue with the Office of Compliance and with me before you take an approval action.

2. If you have a pending application for a product that has other serious deficiencies that cannot be addressed in time for approval by the PDUFA goal date AND there is a pending foreign inspection, it is acceptable to issue an action letter (i.e., and AE letter) and list the ding foreign inspection as an issue that must be resolved prior to roval.

3. If you have a pending application for a "non" important product that is otherwise ready for approval with the exception of the foreign pre-approval inspection (i.e., no other deficiencies that could not be easily worked out to allow for an approval), please discuss this with e Office of Compliance and me before you take an action; either an pproval or an approvable.

I think it is very important that we be consistent in how we approach the issue of delayed pre-approval foreign inspections and I ask your cooperation with the above. Please cc the action letter for all products that have a delayed pre-approval inspection to Kim Colangelo so we can keep track across OND of how often this issue arises. We have faced this situation before and I will ask Kim or Jamie to investigate to see if there is "standard" language that we have used before in this situation in action letters.

John

-----Original Message-----
From: Horowitz, David
Sent: Wednesday, March 26, 2003 6:41 PM
To: Jenkins, John K
Cc: Axelrad, Jane A; Famulare, Joseph; Temple, Robert; Allen, Susan S
Subject: FW: Inspections of "Immediate Public Health Impact"

hn:

The e-mail below should serve as a partial answer to your e-mail of 3/24 (attached). In that message you also asked about going ahead and approving drugs without a pre-approval inspection. We believe that you have authority to approve drugs without a pre-approval inspection, as long as FDA does not have reason to believe that the manufacturing facilities/controls are inadequate to "preserve" the quality of the drug being approved. See 505(d)(3).

In addition, FDAMA added 505(b)~~(4)~~5(F), which provides that "no action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug." Although this language can be read narrowly to expedite an approvable letter (pending completion of the pre-approval inspection), it can also be read to support approval, under appropriate circumstances, without waiting for a delayed preapproval inspection.

However, I strongly recommend that the reviewing division consult with Compliance if they would like to approve a drug without waiting for a pre-approval inspection so that Compliance and review staff can engage in dialog about any known concerns that might significantly affect the quality, safety, or effectiveness of the drug being considered for proval. If such concerns do, indeed, exist, then FDA will be countable for failing to meet the statutory standard for drug approval (505(d)(3)). Although OND is vested with the authority to make this call, 505(b)(4)(E) indicates that compliance division personnel should have the opportunity to demonstrate to the reviewing division why a decision to approve should be modified.

look forward to working with OND to ensure that drug approvals are not unduly delayed despite foreign travel restrictions.

Let me know if you'd like to discuss.

David
<< Message: FW: International Travel - Further Clarification >>

David J. Horowitz, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
301-827-8910 (voice)
301-827-8901 (fax)

-----Original Message-----
From: Famulare, Joseph
Sent: Wednesday, March 26, 2003 5:43 PM
To: Jenkins, John K; Buehler, Gary J; Rivera Martinez, Edwin; Goldberger, Mark J
Cc: Horowitz, David
Subject: Inspections of "Immediate Public Health Impact"

The Office of Compliance has assembled a list of outstanding inspections the attached Excel Spreadsheet. All foreign inspections are postponed until further notice unless they meet the criteria of "Immediate Public Health Impact." Priority NDAs meet this criteria. It is important that any other pending preapproval inspections covering this criteria be identified as soon as possible. Please review the remaining three categories, original NDAs, supplements and generic drugs, to see if any others meet this criteria in light of all issues e.g. supply considerations. Please have someone give this information to Edwin Rivera by noon tomorrow on the remaining three categories in the spreadsheet. ORA needs this information as soon as possible for Investigators that are still abroad and additional people scheduled to leave this Friday. If there are any questions Edwin can be reached at 7-9012 and I can be reached at 7-9036.

Joe Famulare

<< File: Mission Critical - Drugs.xls >>

Mehler, Lynn Whipkey

From: McKelvie, Katlin
Sent: Thursday, February 21, 2008 3:57 PM
To: Mehler, Lynn Whipkey
Subject: CPGs etc - re pre-approval inspections

http://www.fda.gov/cder/dmpq/CPGM7346832.htm
Changes to Compliance Program Guidance Manual (CPGM) 7346.832 and link to the CGP 7346.832 (Preapproval Inspections / Investigations)
http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg490-100.html (scroll to bottom)
Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)

http://www.fda.gov/cder/guidance/4286fnl.htm (GMP guidance for APIs)

http://www.fda.gov/cder/handbook/ (has some useful info)

Katlin McKelvie
Food & Drug Division, OGC
FDA
301-827-1950

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at katlin.mckelvie@fda.hhs.gov.

U.S. Food and Drug Administration

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

Baxter Issues Urgent Nationwide Voluntary Recall of Heparin 1,000 Units/ml 10 and 30ml Multi-Dose Vials

NDC NUMBERS 0641-2440-45, 0641-2440-41, 0641-2450-45 and 0641-2450-41; LOTS: 107054, 117085, 047056, 097081, 107024, 107064, 107066, 107074, 107111

Media Contacts:
Erin Gardiner, (847) 948-4210
Christopher King, (847) 948-4274

FOR IMMEDIATE RELEASE -- DEERFIELD, Ill., January 25, 2008 – Baxter Healthcare Corporation has announced the voluntary recall of nine lots of heparin sodium injection 1000 units/mL 10mL and 30mL multi-dose vials. The company began recalling the lots on January 17, 2008 as a precautionary measure due to an increase in the number of reports of adverse patient reactions that may be associated with the product. Baxter is conducting a thorough investigation of these reports to identify the cause of the increase in allergic-type reactions.

Adverse patient reactions have included: stomach pain or discomfort, nausea, vomiting, diarrhea, decreased or low blood pressure, chest pain, fast heart rate, dizziness, fainting, unresponsiveness, shortness of breath, feeling your heart beat strong or fast, drug ineffectiveness, burning sensation, redness or paleness of skin, abnormal sensation of the skin, mouth or lips, flushing, increased sweating, decreased skin sensitivity, headache, feeling unwell, restlessness, watery eyes, throat swelling, thirst and difficulty opening the mouth. Some of these reactions may be severe or life threatening.

Heparin is a prescription, injectable blood anticoagulant (also called a blood thinner). The 1,000 units/mL multi-dose vials are primarily used for hemodialysis and cardiac invasive procedures. To date, the company has not observed a significant increase in adverse event reports occurring with any other of its heparin presentations.

Customers have been instructed to discontinue use and segregate the recalled product from the rest of their inventory. Customers should then contact Baxter to arrange for return and replacement product. Customers with recalled product purchased indirectly should contact their wholesaler or distributor for return and replacement product. Customers with questions may contact Baxter at 1-800-667-0959. Representatives are available Monday through Friday from 7 a.m. to 6 p.m. CT.

Baxter International Inc. through its subsidiaries, assists healthcare professionals and their patients with the treatment of complex medical conditions, including cancer, hemophilia, immune disorders, kidney disease and trauma. The company applies its expertise in medical devices, pharmaceuticals and biotechnology to make a meaningful difference in patients' lives. For more information about Baxter, visit www.baxter.com.

#

RSS Feed for FDA Recalls Information [what's this?]

Sign up for Recall email updates.

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff

FDA U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

FDA Home Page | CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER

CDER Home | About CDER | Drug Information | Regulatory Guidance | CDER Calendar | Specific Audiences | CDER Archives

Search GO powered by Google™

Questions and Answers on Heparin Sodium Injection (Baxter)

1. What is FDA announcing?

FDA is announcing recent reports of serious allergic-type hypersensitivity reactions and cases of severe hypotension in association with the use of intravenous bolus doses of heparin sodium for injection manufactured by Baxter. In order to minimize the risks associated with use of this product, FDA is providing recommendations to physicians and healthcare providers to avoid bolus dosing with Baxter heparin whenever possible and recommendations for strategies that may limit the occurrence or severity of adverse reactions if the use of heparin is medically necessary and Baxter heparin is the only heparin product available

2. What products and what patients will be affected by this?

Products affected are: Baxter's Heparin Sodium Injection multiple-dose vials (1000 units/mL concentration, 10 mL and 30 mL vials; 5000 units/mL concentration, 10 mL vials; and 10,000 units/mL, 4 mL vials). These are used when patients need large intravenous doses given quickly, sometimes called "bolus doses" in order to thin their blood over a very short period of time. Patients affected are: patients with kidney failure on hemodialysis; patients undergoing certain types of cardiovascular surgery; patients undergoing other specialized treatments called photopheresis and plasmapheresis and some patients who have blood clots in arteries or veins.

3. Are there other patients who may be treated with heparin that this will not affect? (small dose, flush, etc.)

Heparin is used in many other medical settings, but these do not usually require the higher doses that are of concern with the Baxter product. Other uses which are not of concern include small doses of heparin used to flush, or clear out, intravenous catheters or to prevent clotting in indwelling catheters, and slow heparin infusions to treat clotting in various hospital settings.

4. What other companies make heparin and is FDA sure that their product(s) do not have the same risk?

Heparin sodium in multiple dose vials is also manufactured by APP Pharmaceuticals. Hospira and B. Braun also supply some heparin sodium for injection: Hospira in single-use syringes, vials and bags and B. Braun in pre-mixed bags for infusion. FDA is currently investigating whether similar adverse events have been reported for heparin products from other manufacturers.

5. Is APP Pharmaceuticals able to provide enough heparin to avoid a shortage?

Baxter currently manufacturers about 50% of the heparin sodium used in the U.S. Since manufacture of Baxter's multiple-dose heparin sodium vials, which accounts for approximately 75% of Baxter's heparin production, is being suspended, there is a real potential for a shortage of heparin sodium for bolus dosing, especially in the short term. FDA is working with APP and other manufacturers (outside the US) to increase production and/or provide alternate sources of heparin sodium.

6. What kinds of serious adverse events have occurred? How many?

From mid-December 2007 through January 2008 Baxter has received 350 reports of adverse events reported with their product, many of them serious. These include severe allergic reactions, severe nausea, vomiting, diaphoresis, difficulty breathing, and very low blood pressure. Four patients who received heparin bolus during this time died; the relationship between heparin and these deaths is uncertain.

7. When did FDA learn about the adverse events?

FDA learned of the occurrence of adverse events on January 9 from CDC investigators who were evaluating small clusters of these events in dialysis centers. On January 16, 2008, FDA initiated an inspection of Baxter's manufacturing plant in Cherry Hill, New Jersey. At the time of the inspection, Baxter notified the Agency that nine lots of its heparin sodium were being recalled due to an increase in the rate of adverse events with these lots. The recall was initiated on January 17, 2008.

8. Why is FDA not taking the Baxter heparin off pharmacy and hospital shelves, but instead is allowing them to use what product they have?

Heparin sodium is a medically necessary product with some uses for which there are no well-established substitutes. Abrupt withdrawal of all Baxter heparin product would likely lead to severe shortage of heparin sodium for all uses. The increase in occurrence of adverse events with Baxter's heparin appears to be related to administering large amounts of the heparin product over a very short time. An increase in serious reactions has not been seen with use of small amounts and/or slow infusions of heparin sodium. Therefore, the Agency has determined that in the short term, with measures being undertaken to advise caution and careful monitoring of patients receiving heparin, the public health is best served by continued availability of Baxter's existing heparin sodium for clinical situations in which it is needed. The Agency is working with heparin sodium manufacturers to identify and ensure adequate supplies of heparin sodium for future clinical use.

9. What is the cause of the adverse events? What is FDA doing to learn more? When will results of investigations be available?

At this time the cause of the adverse events is unknown. FDA has been working with Baxter and independently to investigate the root cause of the problem since it was first identified and led to the January 17th limited recall. We will continue intensive and in-depth investigation and testing to determine the root cause of the problem.

10. Why did FDA not require Baxter to take this measure at the time of their first recall?

In January it appeared that the adverse events being reported were linked only to a small number of manufacturing lots of Baxter's heparin sodium. Therefore, only those lots were recalled (taken off of hospital and facility pharmacy shelves). However, serious adverse events continued to be reported at an increased rate and involved additional lots of heparin sodium.

11. What other products does Baxter sell? Are any of those products having similar problems?

Baxter sells a wide variety of pharmaceutical products used to treat a number of medical disorders. We have no evidence that the company's other products are associated with an increase in adverse events

12. How is FDA investigating this problem?

We are investigating all possible sources of the problem, including evaluating the active pharmaceutical ingredient manufacturing facility, located in China, and finished dosage form manufacturing facility, located in New Jersey. We will be inspecting these facilities as soon as possible. In addition, FDA is performing comprehensive laboratory analysis of the heparin. FDA is collaborating with the CDC and other experts to determine the root cause of the problem. FDA is also working closely with its international counterparts, in case they have any relevant information

13. What are the alternatives to using the Baxter product?

Heparin sodium in multiple dose vials is also manufactured by APP Pharmaceuticals. Hospira and B. Braun also supply some heparin sodium for injection: Hospira in single-use syringes, vials and bags and B. Braun in pre-mixed bags for infusion. There are other FDA approved anticoagulants, including low molecular weight heparins and direct thrombin inhibitors; however, these products are not approved for use in all the same clinical settings as heparin. There is no experience with the other anticoagulants to achieve the immediate anticoagulation needed for hemodialysis, phereses, and certain cardiac procedures.

14. What should I do if there are no suitable alternative products and my health care provider cannot obtain heparin manufactured by APP?

FDA is recommending that providers consider administering heparin as an infusion rather than a bolus if at all possible. If a heparin bolus is required, FDA recommends that providers use the lowest dose and administer at the slowest rate possible to achieve the desired effect. FDA is advising physicians to monitor patients carefully during the infusion, particularly at the onset, for evidence of allergic reactions, and have resuscitation equipment readily available. FDA is also advising physicians to consider the potential benefits and risks in individual patients of pretreatment with corticosteroids or antihistamines. At this time FDA does not have data to determine if such pretreatment is effective.

15. I received the Baxter product in the past. Am I at risk for a serious reaction?

The serious reactions have generally occurred rapidly; usually within minutes of when the bolus dose was started. However, some patients undergoing cardiac procedures have developed very low blood pressures as late as an hour following the start of the heparin bolus. There is no evidence that the product causes very delayed or late onset allergic reactions.

↑ Back to Top ↖ Back to Heparin

PDF requires the free Adobe Acrobat Reader

Date created: February 11, 2008

FDA U.S. Food and Drug Administration

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

Updated Questions and Answers on Heparin Sodium Injection (Baxter)

Q. What has FDA recently announced about heparin?

A. Adverse events, including deaths, have been associated with the use of heparin, a blood-thinning drug that contained active pharmaceutical ingredient (API) from China. In February 2008, Baxter Healthcare Corporation recalled multi-dose and single-dose vials of heparin sodium for injection as well as HEP-LOCK heparin flush products. After launching a disciplined, methodical examination, FDA scientists have identified a previously unknown contaminant in the heparin. The agency does not have proof that this contaminant is causing the adverse events. There is an association, but not a direct causal link at this time. The agency has made available information on two tests that FDA scientists have conducted to detect the heparin-like substance, and recommend their use to manufacturers and suppliers for screening the heparin API.

Q. What steps has FDA taken?

A. Along with overseeing the recall, FDA scientists have

- Provided recommendations to health care professionals about strategies to limit the occurrence or severity of adverse reactions in cases where the use of heparin is medically necessary and Baxter heparin is the only heparin product available.
- Launched a far-ranging investigation in the United States and abroad.
- Inspected a New Jersey facility to find out whether the heparin could have been contaminated by its packaging.
- Traveled to China to perform a thorough check of the plant that manufactures the heparin ingredient.
- Notified FDA's key regulatory international partners.
- Worked closely with the manufacturer and experts in academia and private laboratories to carry out a thorough chemical analysis of the suspect products. The agency made available information on two tests that FDA scientists have conducted to detect the heparin-like substance, and recommended their use to manufacturers and suppliers for screening the heparin active pharmaceutical ingredient (API).
- Worked to ensure that there exists a safe and adequate supply of heparin to the U.S. market.

Q. What kind of testing did FDA scientists conduct?

A. After conventional testing did not prove useful in detecting these contaminants, FDA experts developed new test methods that use existing state-of-the-art technologies such as nuclear magnetic resonance, capillary electrophoresis, enzymatic kinetics, and bioassay.

Q. What were the results of the testing?

A. FDA scientists determined that the sampled products contained 5 percent to 20 percent of a heparin-like compound—a contaminant that mimicked heparin activity so closely that it was not recognized by routine testing.

Q. How did the contaminant get into the product?

A. At this point, FDA does not know how the contaminant got into the heparin active pharmaceutical ingredient (API). The agency is continuing to aggressively investigate the situation.

For More Information
Information on Heparin Sodium Injection (Baxter)

U.S. Food and Drug Administration

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

Media Transcripts - 2008

PDF documents may be read with a free copy of the Adobe Acrobat Reader.

2008 | 2007

Transcripts of FDA Press Conferences on Adverse Events Associated with Baxter Healthcare Corporation's Multiple-Dose Vials of Injectable Heparin

- March 19, 2008 [pdf 85KB] Audio [3.79 MB MP3]
- March 14, 2008 [pdf 75KB] Audio [4.76 MB MP3]
- March 6, 2008 [pdf 66KB] Audio [4.63 MB MP3]
- March 5, 2008 [pdf 89KB] Audio [5.78 MB MP3]
- February 28, 2008 [pdf 67KB] Audio [4.13 MB MP3]
- February 18, 2008 [pdf 48KB] Audio [3.17MB MP3]
- February 11, 2008 [pdf 49KB]

Transcript of FDA Press Conference on FDA's Early Communication on Botox, Botox Cosmetic and Myobloc

- February 8, 2008 [pdf 64KB] Audio [3.56MB MP3]

Transcript of FDA Press Conference on President's Budget for Fiscal Year 2009

- February 4, 2008 [pdf 36KB]

Transcript of FDA Press Conference on Chantix

- February 1, 2008 [pdf 39KB]

Transcript of FDA Press Conference on Early Communication about an Ongoing Review of Vytorin

- January 25, 2008 [pdf 92KB]

Transcript of FDA Press Conference on Cough and Cold Medicine

- January 17, 2008 [pdf 65KB]

Transcript of FDA Press Conference on Cloning Risk Assessment – Afternoon Media Telecon

- January 16, 2008 [pdf 51KB]

Transcript of FDA Press Conference on FDA Announcement on Final Cloning Risk Assessment

- January 15, 2008 [pdf 51KB] Audio [7.45MB MP3; 43:25 minutes]

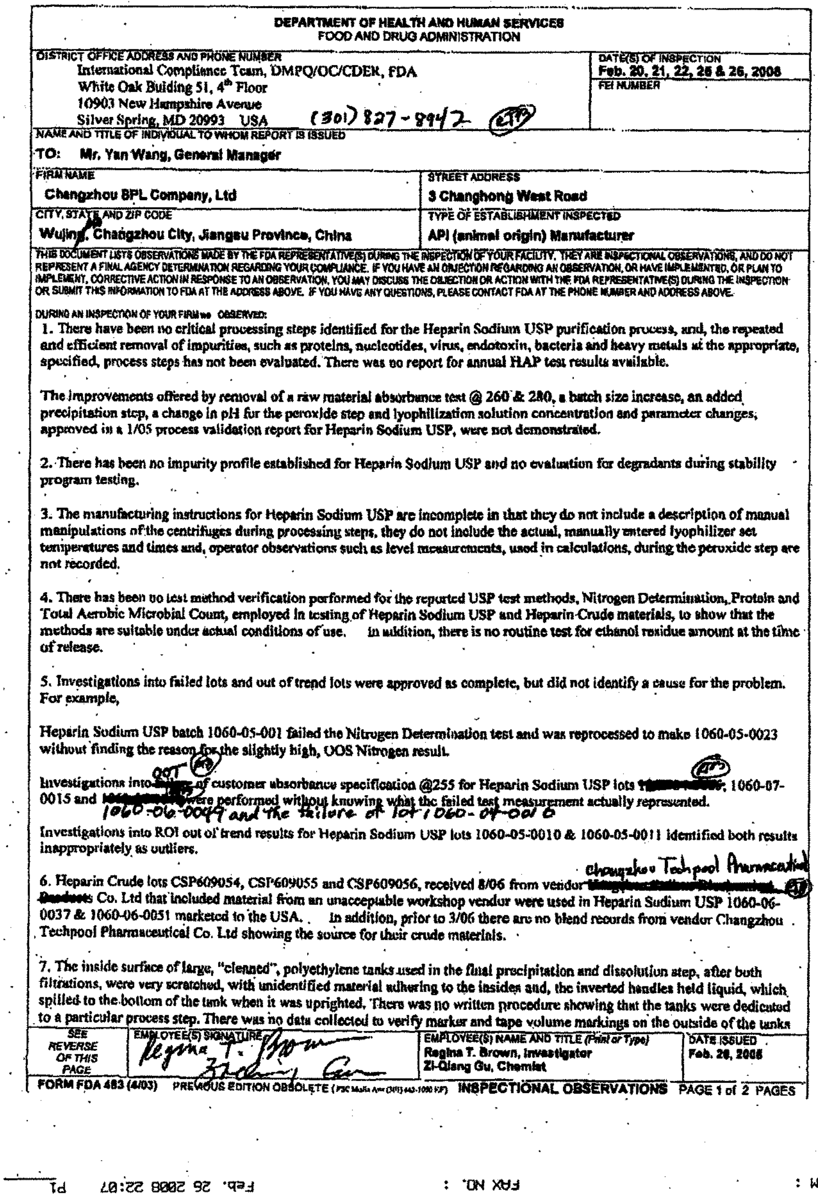
Transcript of FDA Press Conference on FDA Actions on Bio-Identical Hormones

- January 9, 2008 [pdf 98KB]

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
International Compliance Team, DMPQ/OC/CDER, FDA
White Oak Buiding 51, 4th Floor
10903 New Hampshire Avenue
Silver Spring, MD 20993 USA (301) 827-8942

DATE(S) OF INSPECTION: Feb. 20, 21, 22, 25 & 26, 2008

FEI NUMBER:

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Mr. Yan Wang, General Manager

FIRM NAME: Changzhou SPL Company, Ltd

STREET ADDRESS: 3 Changhong West Road

CITY, STATE AND ZIP CODE: Wujing, Changzhou City, Jiangsu Province, China

TYPE OF ESTABLISHMENT INSPECTED: API (animal origin) Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM we OBSERVED:

1. There have been no critical processing steps identified for the Heparin Sodium USP purification process, and, the repeated and efficient removal of impurities, such as proteins, nucleotides, virus, endotoxin, bacteria and heavy metals at the appropriate, specified, process steps has not been evaluated. There was no report for annual HAP test results available.

The improvements offered by removal of a raw material absorbance test @ 260 & 280, a batch size increase, an added precipitation step, a change in pH for the peroxide step and lyophilization solution concentration and parameter changes, approved in a 1/05 process validation report for Heparin Sodium USP, were not demonstrated.

2. There has been no impurity profile established for Heparin Sodium USP and no evaluation for degradants during stability program testing.

3. The manufacturing instructions for Heparin Sodium USP are incomplete in that they do not include a description of manual manipulations of the centrifuges during processing steps, they do not include the actual, manually entered lyophilizer set temperatures and times and, operator observations such as level measurements, used in calculations, during the peroxide step are not recorded.

4. There has been no test method verification performed for the reported USP test methods, Nitrogen Determination, Protein and Total Aerobic Microbial Count, employed in testing of Heparin Sodium USP and Heparin Crude materials, to show that the methods are suitable under actual conditions of use. In addition, there is no routine test for ethanol residue amount at the time of release.

5. Investigations into failed lots and out of trend lots were approved as complete, but did not identify a cause for the problem. For example,

Heparin Sodium USP batch 1060-05-001 failed the Nitrogen Determination test and was reprocessed to make 1060-05-0023 without finding the reason for the slightly high, OOS Nitrogen result.

Investigations into [redacted] OOT of customer absorbance specification @255 for Heparin Sodium USP lots [redacted], 1060-07-0015 and [redacted] were performed without knowing what the failed test measurement actually represented.
1060-06-0049 and the failure of lot 1060-07-0010

Investigations into ROI out of trend results for Heparin Sodium USP lots 1060-05-0010 & 1060-05-0011 identified both results inappropriately as outliers.

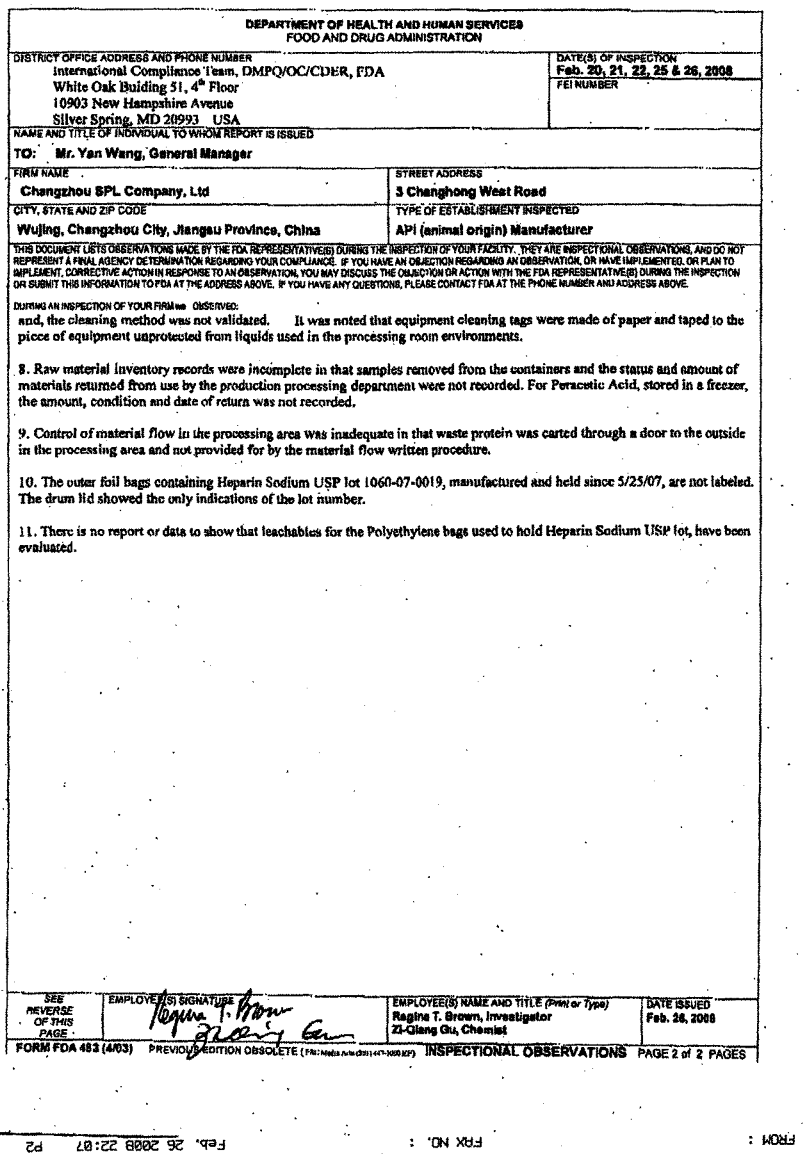
6. Heparin Crude lots CSP609054, CSP609055 and CSP609056, received 8/06 from vendor [redacted] Changzhou Techpool Pharmaceutical Co. Ltd that included material from an unacceptable workshop vendor were used in Heparin Sudium USP 1060-06-0037 & 1060-06-0051 marketed to the USA. In addition, prior to 3/06 there are no blend records from vendor Changzhou Techpool Pharmaceutical Co. Ltd showing the source for their crude materials.

7. The inside surface of large, "cleaned", polyethylene tanks used in the final precipitation and dissolution step, after both filtrations, were very scratched, with unidentified material adhering to the insides and, the inverted handles held liquid, which spilled to the bottom of the tank when it was uprighted. There was no written procedure showing that the tanks were dedicated to a particular process step. There was no data collected to verify marker and tape volume markings on the outside of the tanks

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Regina T. Brown Zi-Qiang Gu	Regina T. Brown, Investigator Zi-Qiang Gu, Chemist	Feb. 26, 2008

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 of 2 PAGES

FROM : FAX NO. : Feb. 26 2008 22:07 P1



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER International Compliance Team, DMPQ/OC/CDER, FDA White Oak Buiding 51, 4th Floor 10903 New Hampshire Avenue Silver Spring, MD 20993 USA	DATE(S) OF INSPECTION **Feb. 20, 21, 22, 25 & 26, 2008** FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: **Mr. Yan Wang, General Manager**	
FIRM NAME **Changzhou SPL Company, Ltd**	STREET ADDRESS **3 Changhong West Road**
CITY, STATE AND ZIP CODE **Wujing, Changzhou City, Jiangsu Province, China**	TYPE OF ESTABLISHMENT INSPECTED **API (animal origin) Manufacturer**

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM we OBSERVED:

and, the cleaning method was not validated. It was noted that equipment cleaning tags were made of paper and taped to the piece of equipment unprotected from liquids used in the processing room environments.

8. Raw material inventory records were incomplete in that samples removed from the containers and the status and amount of materials returned from use by the production processing department were not recorded. For Peracetic Acid, stored in a freezer, the amount, condition and date of return was not recorded.

9. Control of material flow in the processing area was inadequate in that waste protein was carted through a door to the outside in the processing area and not provided for by the material flow written procedure.

10. The outer foil bags containing Heparin Sodium USP lot 1060-07-0019, manufactured and held since 5/25/07, are not labeled. The drum lid showed the only indications of the lot number.

11. There is no report or data to show that leachables for the Polyethylene bags used to hold Heparin Sodium USP lot, have been evaluated.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Regina T. Brown Ziqiang Gu	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* **Regina T. Brown, Investigator** **Zi-Qiang Gu, Chemist**	DATE ISSUED **Feb. 26, 2008**

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 of 2 PAGES

FROM : FAX NO. : Feb. 26 2008 22:07 P2

常州凯普生物化学有限公司
Changzhou SPL Co., Ltd.

March 17, 2008

Food and Drug Administration
International Compliance Team, DMPQ/OC/CDER
Attn: Shawnte Adams
White Oak Building 51, 4th Floor
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Response of Changzhou SPL Co., Ltd. to Form FDA 483 (February 26, 2008)

Dear Sir or Madam:

Enclosed is the response of Changzhou SPL Co., Ltd. ("CZSPL") to the FDA Notice of Inspectional Observations (Form FDA 483) issued on February 26, 2008, following the inspection of our facility from February 20-26, 2008. CZSPL appreciates the professionalism and courtesy with which the FDA investigators conducted the inspection.

CZSPL manufactures the active pharmaceutical ingredient ("API") Heparin Sodium USP (hereinafter "Heparin") for Baxter Healthcare Corporation. Baxter, in turn, uses the API to manufacture Heparin finished drug products. In addition, CZSPL sells crude heparin to its joint venture parent company in the United States, Scientific Protein Laboratories, for purification and processing into API. CZSPL does not manufacture any finished pharmaceutical products at its facility. CZSPL has established a quality system that includes methods, facilities, and controls that comply with the guidelines set forth in FDA/ICH Q7A, "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients."

CZSPL is committed to ensuring the quality of its API products. We established our facility in Changzhou, China in 2001 using modern facilities and equipment specifically for the purpose of producing Heparin API under cGMP conditions. Our facility employs highly qualified personnel who are trained and experienced in quality system principles. CZSPL conducts regular internal audits of our practices, retains outside consultants to inspect our operations, and is periodically audited by our customers. We continually improve our practices based on the results of these audits, updates to compendial standards and methods, and evolving regulatory guidance.

中国江苏省常州市武进区湖塘镇长虹西路 3 号，213161
电话：0519-6560568；传真：0519-6560678；电子邮件：cnczspl@pub.cz.jsinfo.net
3 Changhong West Road, Wujin, Changzhou City, Jiangsu Province, People's Republic of China, 213161
Telephone: +86-519-656-0568; Fax: +86-519-656-0678; Email: cnczspl@pub.cz.jsinfo.net

Some observations in the Form 483 reflect the fact that heparin is a highly complex substance. All heparin manufacturers must therefore contend with the fact that heparin is not technically "well-characterized." For example, observation 2 addresses CZSPL's controls over impurities in the heterogeneous complex of mucopolysaccharides that constitute heparin. To the best of CZSPL's information, however, based on the current scientific knowledge of heparin, the observation cannot be completely addressed at this time. The state of characterization of heparin does not currently permit CZSPL — or other manufacturers of Heparin API — to establish the types of specifications and controls commonly applied to small molecule drugs. This reality is reflected in FDA and ICH GMP guidance, including the FDA-adopted ICH Q6B, "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products," which expressly excludes "heparins" from its scope for the precise reason that heparin cannot be highly characterized using current analytical procedures.

As discussed in greater detail in the attached response, certain of the observations in the Form 483 relate to practices and procedures that CZSPL had self-corrected months or years prior to the FDA inspection. For example, observation 6 in the Form 483 references CZSPL's receipt of three batches of material from an "unacceptable" crude heparin workshop in August 2006. Both finished product lots that CZSPL manufactured using these materials have passed H-1 NMR testing conducted using FDA's recommended method. This observation appears to have arisen from a lack of clarity in how CZSPL presented certain facts during the inspection. Importantly, however, the observation involved events that occurred before CZSPL voluntarily established a system of supplier controls that involves not only direct supplier audits, but audits of each individual crude heparin workshop that provides material to CZSPL's suppliers. This system of directly auditing the suppliers of our suppliers exceeds prevailing industry practices for crude heparin quality control.

Patient safety is our highest priority. To that end, CZSPL remains keenly interested in working with the FDA, the United States Pharmacopeia, academia, and industry in the further study of heparin. As you may be aware, CZSPL has also cooperated fully in the ongoing investigation into the cause of the adverse events reported in certain patients administered heparin products manufactured using API produced by our facility. We want to assure you that we will continue to cooperate in this matter and to share information as necessary and appropriate to protect and promote the public health. For example, CZSPL will adopt the two methods — proton nuclear magnetic resonance (H-1 NMR) and capillary electrophoresis (CE) — that FDA has identified as useful in detecting the presence of an unknown substance potentially associated with adverse events. CZSPL will not release Heparin without employing these two tests. Should the ongoing investigation suggest the advisability of any other changes in our practices or processes, we will move quickly to make those changes.

CZSPL has carefully considered each of the observations in the Form 483. The enclosed response provides our detailed evaluation of the observations, the actions we propose to undertake to address them, and the dates by which we plan to accomplish the actions. We will provide the Agency with periodic updates on our progress in implementing the actions described herein. Please let us know if you need any further information.

Because this submission contains proprietary and highly confidential commercial information and trade secrets, we provide a redacted version of our response. We respectfully request that you use this redacted version for purposes of public disclosure.

Please do not hesitate to contact me at + 86-519-8656-0568 (phone) or +86-519-8656-0678 (fax) should you have any questions regarding this response.

Sincerely,

Yan Wang, Ph.D.
General Manager

cc: Regina T. Brown
Zi-Qiang Gu

Changzhou SPL Co., Ltd.
Response To Form FDA 483 Issued February 26, 2008

March 17, 2008

This document provides Changzhou SPL's ("CZSPL") response to the inspectional observations in the FDA Form 483 issued to our company on February 26, 2008. Each observation is restated below in italics, followed by CZSPL's response. For ease of reference, bracketed identifiers (i.e., [a], [b], [c]) have been added to certain observations that address multiple sub-issues. Where the response provides a date by which a standard operating procedures ("SOP") or work instruction will be "revised," CZSPL will consider the action to be complete only after it has trained its employees on the revised procedure or instruction.

Observation 1

[a] There have been no critical processing steps identified for the Heparin Sodium USP [redacted] *process, and, the repeated and efficient removal of impurities, such as proteins, nucleotides, virus, endotoxin, bacteria and heavy metals at the appropriate, specified, process steps has not been evaluated.*

CZSPL agrees that it is important to identify and evaluate critical processing steps in the [redacted] of Heparin Sodium, USP ("Heparin"). CZSPL's manufacturing instructions [redacted] for the [redacted] of Heparin include detailed instructions for the [redacted] process, from initial crude heparin [redacted] through final [redacted] Heparin [redacted]. Each critical phase in the Heparin [redacted] process ([redacted], [redacted], and [redacted]) is described in detail with regard to critical process control parameters.

CZSPL conducted two successful process validation studies, one in 2002 [redacted] and the other in 2004 [redacted]. For both process validations studies, CZSPL identified the following critical process steps.

A total of three Heparin batches were used in the 2002 process validation. The study included 87 in-process validation tests designed to measure the removal of impurities (proteins, nucleotides, and heavy metals), naturally-occurring biological contaminants (bacteria and endotoxin), and Heparin potency. In addition, a total of 54 finished product tests were conducted for the validation batches (18 tests per batch). These tests included all United States Pharmacopeia ("USP") requirements for Heparin, [redacted] testing for protein and nucleotide impurities, and additional customer-required testing.

A total of three Heparin batches were used in the 2004 process validation. In addition to the critical steps, this study measured the protein and nucleotide removal capability of [redacted] more process steps. A total of 168 in-process tests were performed (protein, [redacted], heavy metals, endotoxin, bioburden, and potency). In addition, 63 finished product tests were conducted (21 tests per batch). These tests included all USP requirements for Heparin, [redacted] testing for protein and nucleotide impurities, and additional customer-required tests.

For both process validation studies, all in-process tests met their respective pre-defined requirements, thus demonstrating repeated and effective removal of impurities and naturally-occurring biological contaminants. All finished Heparin test results also met their respective specification limits.

A comprehensive viral inactivation study was previously conducted by CZSPL's joint venture parent company, Scientific Protein Laboratories LLC ("SPL"), which demonstrated that the process can efficiently inactivate a wide cross-section of viruses. Model viruses used in the study were selected for their pertinent properties, including [redacted] versus [redacted], [redacted], [redacted], and [redacted]. The results of the study and its applicability to CZSPL's Heparin process are included in Attachments 1 and 2.

In reviewing the process validation documentation for this response, we agree that critical processing step identification and evaluation information could be presented more clearly. For this reason, we will revise our validation SOP [redacted], "Outline for Validation Protocols and Reports," to require more specific identification of critical process steps and the evaluation of the related test results. In addition, once the equipment changes and software upgrade described in response to Observations 3 and 7 have been completed, CZSPL will develop and execute a new process validation protocol for the manufacture and [redacted] of Heparin Sodium USP. This protocol will include clear and comprehensive identification of all critical processing steps.

Action	Date
Revise validation procedure [redacted], "Outline for Validation Protocols and Reports," to require more specific identification of critical process steps and evaluation of the related test results.	April 30, 2008
Complete a new process validation for the manufacture and [redacted] of Heparin Sodium USP, using new [redacted].	December 31, 2008

[b] There was no report for annual [redacted] *test results available.*

CZSPL's joint venture parent company SPL submits samples of crude heparin from its suppliers to an outside laboratory for annual [redacted] testing. These suppliers include those who supply crude heparin to CZSPL. The results from these samples were acceptable for each year of production. A summary of these test results is provided in Attachment 3.

To ensure that the annual [redacted] results are made available and evaluated locally, CZSPL will revise SOP [redacted], "Annual Product Review," to require the inclusion of HAP results in the annual product review. CZSPL will also include these results in the annual update to the DMF.

Action	Date
Revise SOP [redacted], "Annual Product Review," to require the inclusion of [redacted] results in the annual product review.	April 30, 2008
Revise SOP [redacted], "Drug Master File Change Control," to specify the information to be reported to SPL for the annual update to CZSPL's DMF, including [redacted] testing results.	April 30, 2008

[c] The improvements offered by removal of a raw materials [redacted] test [redacted], a batch size increase, an added [redacted] step, a change in [redacted] for the [redacted] step and [redacted] and parameter changes, approved in a 1/05 process validation report for Heparin Sodium USP, were not demonstrated.

CZSPL respectfully disagrees with the observation that the manufacturing process improvements adopted in 2005 "were not demonstrated" in the process validation study. The improvements were designed to allow for an increase in [redacted], eliminate certain process inefficiencies, and demonstrate a more robust process for eliminating [redacted] impurities. The validation study successfully demonstrated that the changed process was operating in a state of control and consistently met all applicable requirements.

CZSPL will re-institute specification limits for [redacted] testing [redacted] for crude heparin. These limits will be based on data from the most recent process validation, conducted in 2004, and will also take historical data into account. Re-instituting the [redacted] test limits will provide added assurance and control over the quality of incoming crude heparin used in manufacturing Heparin Sodium USP.

Action	Date
Provide an addendum to the January 2005 process validation report to fully describe process-related improvements.	April 30, 2008
Re-institute the [redacted] test [redacted].	April 30, 2008

Observation 2

There has been no impurity profile established for Heparin Sodium USP and no evaluation for degradants during stability program testing.

The current CZSPL testing regimen for heparin sodium is consistent with industry practice reflected in ICH Q7A § 11.2, which states that "Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin." The complexity of the investigation into the heparin product recently recalled by SPL and Baxter Healthcare Corporation demonstrates the difficulty of isolating and identifying impurities in heparin due to the nature of the heterogeneous mixture of mucopolysaccarides. Just days ago, FDA announced a recommendation that heparin manufacturers adopt two advanced methods — proton nuclear magnetic resonance (H-1 NMR) and capillary electrophoresis (CE) — for their potential utility in detecting an unknown substance seen in lots of Heparin product potentially associated with adverse events.

CZSPL will add FDA's interim recommendation for the H-1 NMR and capillary electrophoresis testing to its routine release testing for Heparin Sodium USP and will adopt any other tests to be required by FDA. As an additional measure, CZSPL will develop and evaluate the use of [redacted] for its Heparin Sodium USP.

CZSPL is committed to the continued evaluation of new analytical tools for the improved characterization of heparin.

CZSPL has well-defined impurity profiles for all non-mucopolysaccharide impurities, according to industry practice. These profiles, which meet the criteria set forth in ICH Q7A § 11.2, include proteins, heavy metals, and process chemicals such as [redacted]. Naturally-occurring biological contaminants (including endotoxin and total aerobic plate count) are also routinely trended. These data are documented in each year's Annual Product Review, as recommended by ICH Q7A, and are summarized in Attachment 4.

Based on our review of this observation, CZSPL has identified opportunities for improving our documentation practices. CZSPL will Revise SOP [redacted], "Drug Master File Change Control," to require that CZSPL include an impurity profile update in each DMF annual report.

Action	Date
Develop an SOP to adopt H-1 NMR and CE test methods recommended by FDA as routine release tests; amend the release specification accordingly.	Before the next release of any Heparin product.
Develop and evaluate the use of [redacted] for Heparin Sodium USP.	December 31, 2008
Revise SOP [redacted], "Drug Master File Change Control," to require that CZSPL include an impurity profile update in each DMF annual report.	April 30, 2008

Observation 3

The manufacturing instructions for Heparin Sodium USP, are incomplete in that they do not include a description of manual manipulations of the [redacted] *during processing steps, they do not include the actual, manually entered* [redacted] *set temperatures and times and, operator observations such as level measurements, used in calculations, during the* [redacted] *step are not recorded.*

To address this observation, CZSPL will revise the SOPs and Manufacturing Instructions [redacted] to add more detailed instructions for [redacted] operations and require the recording of [redacted] settings as well as raw level data and calculations for the [redacted] manufacturing step. These changes will be implemented prior to the next production campaign. In addition, CZSPL will upgrade the control software for the [redacted] to reduce manual operations, qualify the [redacted] and computer system with the upgraded software, and revise SOP [redacted] and Manufacturing Instructions [redacted] accordingly.

Action	Date
Revise SOP [redacted] to add detailed instructions for [redacted] operators.	March 31, 2008
Revise Manufacturing Instructions [redacted] to require the recording of [redacted] temperatures and set times as well as raw level data and calculations for the [redacted] manufacturing step.	March 31, 2008
Upgrade the control software for the [redacted] to reduce manual operations, revise SOP [redacted], and Manufacturing Instructions [redacted], and perform Installation Qualification and Operational Qualifications.	May 31, 2008

Observation 4

There has been no test method verification performed for the reported USP test methods, Nitrogen Determination, Protein and Total Aerobic Microbial Count, employed in testing of Heparin Sodium USP and Heparin Crude materials, to show that the methods are suitable under actual conditions of use. In addition, there is no routine test for [redacted] *amount at the time of release.*

CZSPL's QC laboratory performed basic test method suitability tests on the CZSPL heparin sodium API in accordance with CZSPL SOPs for all of the parameters cited in the observation (Nitrogen Determination, Protein, Total Aerobic Microbial Count, and [redacted]). To address the FDA Investigators' observation to enhance its verification for the Nitrogen Determination and Total Aerobic Microbial Count test methods, CZSPL will add a [redacted] step to the verification for Nitrogen Determination and repeat the test for Total Aerobic Microbial Count using the [redacted] in accordance with USP <61>, "Antimicrobial Preservative Effectiveness Testing."

With respect to the USP test method for protein, USP <1226>, "Verification of Compendial Procedures," states that verification is not required for "basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test." CZSPL considers the USP protein test to be a basic compendial test. To add a quantitative measurement for protein, CZSPL will adopt the Heparin Sodium [redacted] as a requirement for routine release testing.

[redacted]. Nevertheless, as an added measure, CZSPL will implement the use of [redacted] testing for [redacted] at the time of release. CZSPL has previously validated this test method.

Action	Date
Add a [redacted] step to the verification for Nitrogen Determination.	June 30, 2008
Repeat the test for Total Aerobic Microbial Count using the [redacted] in accordance with USP <61>.	June 30, 2008
Adopt Heparin Sodium [redacted] for routine product release testing.	June 30, 2008
Implement [redacted] testing for [redacted] at the time of release.	June 30, 2008

Observation 5

Investigations into failed lots and out of trend lots were approved as complete, but did not identify a cause for the problem. For example,

[a] Heparin sodium USP batch [redacted] failed the Nitrogen Determination test and was reprocessed to make [redacted] without finding the reason for the slightly high, OOS Nitrogen result.

[b] Investigations into OOT of customer [redacted] specification [redacted] for Heparin Sodium USP lots [redacted] and [redacted] and the failure of lot [redacted] were performed without knowing what the failed test measurement actually represented.

[c] Investigations into ROI out of trend results for Heparin Sodium USP lots [redacted] & [redacted] identified both results inappropriately as outliers.

CZSPL acknowledges the importance of performing thorough root-cause investigations for Out-of-Specification (OOS) and Out-of-Trend (OOT) results. SOP [redacted], "Laboratory Investigations and Data Handling," prescribes the steps to be followed when CZSPL conducts such investigations. While it is always the goal of OOS and OOT investigations to identify a root cause, sometimes the investigation cannot identify root cause. This is particularly true for API's of animal origin where analytical characterization is constrained due to API complexity. In the investigations described in observations 5[a] and [b], CZSPL followed internal procedures, conducted thorough investigations, and applied scientific judgment in making product disposition determinations. Observation 5[c] describes a use of an [redacted] test that is no longer permitted under a revision of SOP [redacted] that took effect on August 31, 2007, nearly six months before the FDA inspection.

The specific examples cited in the observation are discussed below in greater detail:

[a] Analytical Laboratory Investigation [redacted] documents the findings for a Nitrogen OOS result for batch number [redacted]. It was determined that there were no verifiable laboratory errors to explain the original results; therefore, the initial conduct of the test was deemed valid. Retesting ([redacted] preparations) was performed by two different analysts, for confirmation of the initial results. The retest results, which were found to be [redacted] within the acceptance limits of 1.3 – 2.5% for nitrogen, were [redacted].

A manufacturing process investigation, [redacted], was conducted to assess whether there were any processing errors or deviations that might explain the [redacted] results. The investigation determined that there were no documented processing errors. Batch run parameters were consistent with other lots produced using the same manufacturing process [redacted].

Based on a historical review, the initial OOS results appear to be an isolated incident with no clear assignable cause. Since the retest results were within specification, although [redacted], the decision was made to reduce the nitrogen content of the batch using a written re-processing protocol and allowed for in the DMF. The re-processed batch was identified as [redacted] and was processed using protocol [redacted]. Quality Assurance released the reprocessed batch on December 2, 2005, after generating three months of acceptable stability data. The batch had a reported nitrogen content of [redacted]% (dried basis), which was well below the upper limit of 2.5%. CZSPL believes that this investigation, re-processing protocol, and release decision complied with applicable SOPs and cGMP standards.

[b] Customer specification [redacted] requires the performance of a test for [redacted] in addition to USP requirements. Atypical results that were within the customer specification but out of trend for batches [redacted] and [redacted] were documented in [redacted] and [redacted], respectively. The preliminary analytical investigations did not identify any laboratory-related errors that would explain the initial results or invalidate the conduct of the tests. In accordance with the retest scheme outlined in SOP [redacted], [redacted] additional samples were tested, which confirmed the original atypical results. For both batches, the initial test results were confirmed by the retesting.

Batch record investigations, [redacted] and [redacted], were performed to assess whether processing errors or deviations may have contributed to the atypical data. The investigations determined that both lots were manufactured without incident and were consistent with other lots produced. Since the investigations did not identify an assignable cause for the atypical results and all test values met customer specification, the batches were released for distribution.

The observation also relates to batch [redacted], which was later reprocessed, according to the procedure in the DMF, into batch [redacted]. Batch [redacted] was investigated for an OOS result in [redacted]. The OOS results were determined to be valid and were later confirmed with appropriate retesting. Quality Observation Report [redacted] documents the production record investigation, which determined that the batch was manufactured using the revised and validated process [redacted]. Review of the pertinent batch documentation revealed that there were no processing errors or other deviations during production of the batch. It was noted, however, that the crude raw material used to produce this batch came from a new supplier that was qualified using Material Evaluation Protocol [redacted]. Batch [redacted] was the only batch produced using the new crude material before this new supplier was re-evaluated in 2007.

Since the investigations failed to identify an assignable cause for the OOS results, the decision was made to reprocess [redacted]. The material was successfully reprocessed as batch number [redacted] using protocol [redacted]. Quality Assurance released the reprocessed batch on May 20, 2005 with a reported [redacted]. The result was well below the customer specification of [redacted] for the test.

[c] Investigations of OOT Residue on Ignition (ROI) test results for batches [redacted] and [redacted] were documented in [redacted] and [redacted], respectively. CZSPL acknowledges that the [redacted] test should not have been used to invalidate extreme ROI data points in these investigations, as provided in FDA guidance for such chemical tests. As noted above, the use of an [redacted] test is no longer permitted under a revision of SOP [redacted].

CZSPL's current SOP on laboratory investigations, [redacted], effective on August 31, 2007, specifically provides instructions for the handling of statistical [redacted] tests to invalidate data points for chemical tests like the ROI test. The referenced OOT results were generated on April 26, 2005 and March 23, 2006, which pre-dates the current procedure.

The acceptance limits for the ROI test are 28.0 – 41.0% and, in both instances, the atypical results were within the range for acceptance. Since the [redacted] test was inappropriately applied, CZSPL will clarify investigation reports [redacted] and [redacted] to state that the atypical results are not invalid for the two affected lots. Additionally, an investigation will be performed to determine whether the [redacted] test was applied for similar chemical tests affecting other lots.

Action	Date
Clarify investigation reports [redacted] and [redacted] to state that the atypical results are not invalid. Correct any associated documentation for lots [redacted] and [redacted].	March 31, 2008
Investigate to determine whether the [redacted] test was applied for chemical tests affecting other lots and correct investigations as appropriate.	March 31, 2008

Observation 6

[a] *Heparin Crude lots [redacted], [redacted] and [redacted], received 8/06 from vendor [redacted] that included material from an unacceptable workshop vendor were used in Heparin Sodium USP [redacted] marketed to the USA.*

CZSPL did not in fact receive and use material from an "unacceptable" workshop. This observation appears to have arisen from a lack of clarity in how CZSPL presented certain facts during the inspection.

The observation references three lots of crude heparin received from CZSPL's direct supplier, or "consolidator," of crude heparin, [redacted], in August 2006, which CZSPL used to manufacture product lots [redacted] and [redacted]. (In March 2008, samples from both lots have passed H-1 NMR testing conducted using FDA's recommended method.)

In August 2006, when the lots of crude heparin at issue were received, CZSPL was in the process of establishing a new system for qualifying its consolidators by auditing not only the consolidators themselves, but also each individual workshop that provided crude heparin to the consolidators. CZSPL developed this program in an effort to achieve a level of control that exceeded prevailing industry practices for qualifying crude heparin suppliers.

CZSPL initiated its supplier qualification efforts in the fall of 2005 by conducting "pre-audits" of workshops identified by [redacted]. These pre-audits were essentially a survey of industry practices designed to gather information that would enable CZSPL to establish uniform standards for individual workshops. Before initiating official audits to qualify individual workshops, in June 2006 CZSPL issued SOP [redacted], "New Crude Heparin Supplier Approval," which established CZSPL's standards and procedures for formally auditing crude heparin workshops. This SOP provided that CZSPL would examine each workshop's facilities, equipment, sanitation, processes for receiving raw materials and intestines, production, laboratory, documentation practices, and representative slaughterhouse operations. CZSPL then conducted formal qualification audits of individual workshops identified by [redacted] in accordance with a protocol, [redacted], "Material Evaluation

Protocol, Requalification Crude Heparin Supplier; [redacted]." These audits ran from September - November 2006.[1]

The observation in the Form 483 appears to have resulted from CZSPL's lack of clarity, during the FDA inspection, in distinguishing between the "pre-audits" and formal qualification audits. The workshop described as "unacceptable" in the observation had been the subject of a pre-audit in October 2005. The pre-audit found that the workshop needed to establish and improve its document management and tracking system before being accepted. This pre-audit finding did not, however, mean that the workshop was "unacceptable." • Indeed, a number of other workshops had similar observations relating to their documentation practices at the pre-audit stage, but were ultimately approved after implementing corrective actions prior to their formal qualification audits.

The workshop referenced in the observation ultimately was not approved because [redacted] never requested that CZSPL formally audit it. CZSPL understands [redacted] decision not to seek qualification of this workshop (and several others) to have been based on the latter's lack of cooperation in addressing the pre-audit findings. This decision had not, however, been made in August 2006, as the full formal auditing program had not even begun.

In sum, use of the lots referenced in the observation was not a violation of CZSPL's policies in place at the time. CZSPL was striving to achieve a level of control over crude heparin workshops that exceeded prevailing industry practices. This process took a significant amount of time and resources. The Form 483 observation relates to events that occurred while this effort was underway, but before it had been completed. Today, CZSPL has in place a documented system for crude heparin quality control that involves auditing and approval of each crude heparin workshop before it can supply one of CZSPL's consolidators.

[b] *In addition, prior to 3/06 there are no* [redacted] *records from vendor* [redacted] *showing the source for their crude materials.*

Prior to March 2006, [redacted] [redacted] records included the [redacted] name of the workshops that produced crude heparin. In March 2006, CZSPL began requiring [redacted] to identify the individual batch numbers on the [redacted] records and to keep information providing a full audit trail to the individual workshop level.

Observation 7

The inside surface of large, "cleaned", [redacted] *tanks used in the final* [redacted] *and* [redacted] *step, after both* [redacted] *were very scratched, with unidentified material adhering to the insides and, the inverted handles held liquid, which spilled to the bottom of the tank when it was uprighted. There was no written procedure showing that the tanks were dedicated to a particular process step. There was no data collected to verify marker and tape volume markings on the outside of the tanks and, the cleaning process was not validated. It was noted that equipment cleaning tags were made of paper and taped to the piece of equipment unprotected from liquids used in the processing room environments.*

---

[1] A final audit for one workshop was conducted in July 2006, before the full auditing program began.

To enhance its equipment and procedures further, CZSPL will:

- Replace the [redacted] [redacted] tanks used in the final precipitation and solubilization step with one [redacted]. This [redacted] [redacted] will be equipped with Clean in Place technology and an automated level reader, which will eliminate the need for the volume markings on the outside of the tanks.
- Replace the [redacted] [redacted] tank with a [redacted]. This [redacted] will continue to be dedicated for transferring material for loading into the [redacted], as provided in SOP [redacted], "Tank Transfer System for Heparin Sodium [redacted]," [redacted].
- Develop cleaning methods for the new tanks.
- Perform cleaning validation on the new cleaning methods for cleaning the vessels.
- Revise SOPs [redacted], "Heparin [redacted] Area and Equipment Cleaning," and [redacted], "Tank Transfer System for Heparin Sodium [redacted]," and Manufacturing Instructions [redacted] to specify dedicated use, use instructions, and cleaning instructions.
- As an interim measure, replace the existing [redacted] tanks with new [redacted] tanks and conduct cleaning validation on the new tanks using the manual cleaning methods after each cleaning.
- Identify and implement the use of new equipment status tags with proper protection from exposure to liquid and proper attachment materials.

Action	Date
Replace existing four [redacted] [redacted] tanks with one [redacted]. Develop or revise SOPs as appropriate.	September 30, 2008
Replace the [redacted] [redacted] tank with one [redacted]. Develop or revise SOPs as appropriate.	June 30, 2008
Conduct cleaning validation on new cleaning methods for [redacted].	First three batches of production using the [redacted].
Revise relevant SOPs to specify dedicated use, use instructions and cleaning instructions for both new vessels.	March 31, 2008

Action	Date
As an interim measure, replace existing [redacted] tanks with new [redacted] tanks.	Prior to next production campaign
Conduct cleaning validation on the new [redacted] tanks.	First three batches of next production campaign
Implement use of new equipment status tags with protective enclosure and appropriate attachment.	Prior to the next production campaign

Observation 8

[a] Raw material inventory records were incomplete in that samples removed from the containers and status and amount of materials returned from use by the production processing department were not recorded.

To address the observation, CZSPL will:

- Revise SOP [redacted], "Requisition of Raw Materials from the Warehouse," by adding the requirement that, after QC sampling, sampling information such as amount sampled, container number, date sampled, sampled by, and lot number be recorded on the inventory control record;

- Revise the inventory control record by adding detailed dispensing information, such as dispensed container number and the remaining amount in partially dispensed container; and

- Revise SOP [redacted] to provide that, if unused material is returned to the warehouse from the production area, the warehouse must verify and document the quantity and the intactness of the packaging. Partially used containers shall not be returned to the warehouse unless the opening of those containers has been witnessed and documented by both a warehouse employee and the user who requisitioned the material.

[b] For [redacted] stored in a freezer, the amount, condition and date of return was not recorded.

CZSPL will revise SOP [redacted] to specify detailed procedures for the dispensation and return of unused partial containers of [redacted]. The revised SOP will include an inventory control log to record, for each container, the container number, the time of dispensation and the amount dispensed, the time and the amount of the return, and the [redacted] of the returned [redacted]. The maximum time duration from dispensation to return of the [redacted] will be specified. The [redacted] of the returned [redacted] shall not exceed [redacted]. Returned [redacted] that fails to meet these requirements shall be rejected.

Action	Date
Revise SOP [redacted].	April 30, 2008

Observation 9

Control of material flow in the processing area was inadequate in that waste [redacted] was carted through a door to the outside in the processing area and not provided for by the material flow written procedure.

CZSPL will take actions to improve material flow in the processing area and further define its material flow practices in written procedures. The company will construct a new partition to separate the exterior door referenced in the observation from the processing area to prohibit unauthorized access to the facility, as well as to prevent the production area from direct exposure to the outside environment.

CZSPL will amend relevant SOPs ([redacted], "Clean-up for Manufacturing Area," [redacted], "Personnel Movement and Dress Code Requirements in the Workshop," and [redacted], "Material Movement and Handling Requirements in the Workshop") and applicable facility maps.

Action	Date
Construct a partition to separate the exterior door from the processing area and revise SOPs [redacted], [redacted], and [redacted].	April 30, 2008
Revise applicable facility maps.	April 30, 2008

Observation 10

The outer foil bags containing Heparin Sodium USP lot [redacted], manufactured and held 5/25/07, are not labeled. The drum lid showed the only indications of the lot number.

To address this observation, CZSPL will revise its current manufacturing instructions [redacted] to require that labels indicating the unique lot number and container number be affixed on the outside of each of the [redacted] [redacted] bags, the outside of the [redacted] bag, the top of the drum lid, and the outside wall of the drum.

Action	Date
Revise current manufacturing instructions [redacted] to require that labels indicating the unique lot number and container number be affixed on the outside of each of the [redacted] bags, the outside of the [redacted] bag, the top of the drum lid, and the outside wall of the drum.	March 31, 2008

Observation 11

There is no report or data to show that leachables for the [redacted] *bags used to hold Heparin Sodium USP lot, have been evaluated.*

CZSPL uses pharmaceutical grade [redacted] bags imported from the U.S. for product packaging. CZSPL will conduct USP [redacted] [redacted] testing for the [redacted] bags used to hold Heparin Sodium USP. USP Chapter [redacted] provides applicable standards for plastic materials and components used to package pharmaceuticals. This testing will include an evaluation of extractables, heavy metals, nonvolatile residue, differential scanning calorimetry (thermal analysis), and IR spectroscopy. This approach should provide ample information with which to evaluate the polyethylene bags.

Action	Date
Develop and execute a protocol to submit the [redacted] bags used to hold Heparin for USP [redacted] testing for extractables and other requirements.	September 30, 2008

Changzhou SPL Co., Ltd.

Index of Attachments

Attachment	Document Name
1	Risk Management For Heparin Sodium
2	Comparison of Heparin Sodium USP Manufacturing Processes 1037, 1035, 1060 for Viral Validation Consideration
3	HAP Test Results 2004-2006
4	Heparin Sodium USP 1060 Impurity Profile

Changzhou SPL Co., Ltd.

Attachment 1

Risk Management For Heparin Sodium

Redacted

Changzhou SPL Co., Ltd.

Attachment 2

Comparison of Heparin Sodium USP Manufacturing Processes 1037, 1035, 1060 for Viral Validation Consideration

Redacted

Changzhou SPL Co., Ltd.

Attachment 3

Herbicides, Antibiotics, Pesticides (HAPS) Test Results 2004-2006

Note: 2007 results have not yet been received from the contract laboratory

Redacted

Changzhou SPL Co., Ltd.

Attachment 4

Heparin Sodium USP 1060 Impurity Profile

Redacted

Establishment Inspection Report
Changzhou SPL Company, Ltd.
Changzhou, China (Mainland)

FEI: 3003335664
EI Start: 02/20/2008
EI End: 02/26/2008

SUMMARY OF FINDINGS

This inspection of an active pharmaceutical ingredient manufacturer was initiated as a directed inspection, FACTS Assn. Id. 928692, Op. Id. 3625457, as a follow up to Baxter recalls and CDER requested coverage of Heparin Sodium; this firm is a manufacturer and tester of Heparin Sodium USP and Heparin Sodium Crude that are used in sterile finished dosage forms that are being recalled, nationwide. The firm has filed DMF #15973. This inspection covered all Quality Systems. Twenty eight samples from retained materials were collected.

This was the initial inspection of this facility.

This inspection found that process validation for the purification of Heparin Crude was inadequate in that there were no critical process steps identified for control of the process, the stepwise removal of impurities such as heparin degradation products, protein, nucleotide, virus, bacteria, heavy metals and endotoxin has not been evaluated and to date using test methods that have not been established as suitable for the conditions of use. In addition, during 1/05, process changes were approved that included removal of Heparin Crude quality attributes based on the ease of procurement and without adequate raw material evaluation. Heparin Crude received since the 2004 changes, have shown increased Absorbance values at 260nm. In addition, the inspection found that the impurity profile for the Heparin Sodium USP had not been established and that a discontinued workshop's crude heparin had been included several 7-8/06 Heparin Crude lots purchased by this firm from Changzhou Techpool, put through the 1060 process and one API lot sold to SPL. Other deficiencies included equipment that was not cleaned, non-specific manufacturing instructions. An FDA483 was issued 2/26/08 to Dr. Yan Wang, General Manager at the firm, who stated that a written response with a timeline for corrections would be submitted.

ADMINISTRATIVE DATA/HISTORY OF BUSINESS/INDIVIDUAL RESPONSIBILITY/PERSONS INTERVIEWED

On 2/20/08 I, Regina T. Brown, Investigator, NWJ-DO, Dr. Zi-Chiang Gu, Chemist, OC, CDER, Ms. Li Xia Wang, Senior Health Specialist, HHS, Embassy Beijing and Mr. Bruce Ross, Health Attaché, HHS, Embassy Beijing identified ourselves to Dr. Yan Wang, General Manager and began the inspection. In addition to the firm personnel listed below, we were also greeted by 5 SFDA officials, who offered their assistance to the team. They were: Mr. Qing Wu Guo, Division of Production Safety, Department of Drug Regulatory (Beijing), Mr. Yuen Liu, Drug Center (Nanjing), Mr. Yue Wang (Jiangsu), Mr. Wei Chen, GMP Inspector (Nanjing) and Ms. Bei Xue, Deputy Director (Changzhou). After the introductions, clarification of the status of the SFDAers as guests of the firm and an explanation of the scope of the inspection, Mr. W. Chen was designated to observe for the entire inspection. Dr. Y. Wang stated that this firm was not registered with the SFDA as a pharmaceutical manufacturer. On 2/21 & 22/08 Ms. Liu Jing, Staff Member, Division of

Cooperation (Beijing) also observed the inspection. Ms. L. Wang participated as a translator through 2/22/08. CSO Brown, Chemist Gu and HA Ross were present for all inspection dates.

Dr. Yan Wang, Ph.D., General Manager (GM) for this firm (Exh. 1 pg. 1, 2 & 3), stated that he spent about 15% of his time at this facility in China. He stated that his other title, Vice President, Business Development and Research was his title at his office at the Waunakee, WI Scientific Protein Laboratories LLC facility (SPL). He stated that the current establishment had only one name and that as written in Chinese, the name sounded like "Kayeepoo." Dr. Y. Wang stated that his routine communications with the firm were financial only and were with Mr. Yuncia Zhu, Senior Manager (Exh. 1 pg. 1). Dr. Y. Wang stated that his signature was necessary for all Changzhou SPL purchases. He stated that he was not an expert in the chemistry of Heparin.

Inspected firm:	Changzhou SPL Company, Ltd.
Location:	3 Changhong West Rd., Hutang Township, Wujin City Changzhou, China (Mainland)
Phone:	
FAX:	
Mailing address:	3 Changhong West Rd., Hutang Township, Wujin City Changzhou, China (Mainland)
Dates of inspection:	2/20/2008, 2/21/2008, 2/22/2008, 2/25/2008, 2/26/2008
Days in the facility:	5
Participants:	Regina T. Brown, Investigator

Dr. Y. Wang identified himself as the most responsible person at the firm. He was the person to whom all correspondence should be addressed. He stated that there were 33 firm employees and that all operations except production were 1 12-hour shift per day for 6 days a week. The 10 Production Department personnel worked in two shifts. There was no production of Heparin Sodium USP during this inspection, because the RO water System had sprung a leak over the Spring Festival holiday, which had just ended.

Dr. Y. Wang provided us with organizational chart (Exh. 1 pg. 1) showing that the QA Director and the Operations Assistant General Manager reported to him. He showed paper certifying his appointment as General Manager (Exh. 1 pg. 3), and stated that he reported to Mr. David Strunce, President & CEO (Exh. 1 pg. 2), Scientific Protein Laboratories LLC (SPL). Mr. D. Strunce was also Chairman of the Board of Directors for Changzhou SPL Co. Ltd (CZSPL). Mr. D. Strunce reportedly maintained an office at the 700 East Main St., Waunakee, WI 53597 SPL location. Dr. Y. Wang also had an office at that location.

Dr. Y. Wang stated that CZSPL was a joint venture and 55% owned by SPL and that CZSPL was 45% owner of a joint venture with Changzhou Techpool Pharmaceutical Co. Ltd. (CT), located next door. He stated that the SPL Acquisition Corp. (Exh. 1 pg. 2) was owned by American Capital (Exh. 1 pg. 4-5); the Officers, Directors and Managing Directors were identified to us, the head office is at 2 Bethesda Metro Center, 14th Floor, Bethesda, MD 20814. CZSPL had no outside US Agents. The amount of heparin API sent to the USA was provided in a list (Exh. 2).

The following persons, as well as Dr. Y. Wang, provided the bulk of information during the inspection:

Ms. Denise L. Kwiatkowski, Regulatory Affairs Manager, who stated that she had put together the DMF for the facility. She provided the viral study information and obtained some summary information about these studies, which were done in 1997, 1998 and 2002.

Mr. Ruan Wenxing, QA Director (Exh. 1 of 1), was present throughout the inspection and provided responses to questions about testing, batch records and test records. He was in charge of the four persons in QA and was knowledgeable about the day to day operations at the firm.

Mr. He Xianfeng , Assistant to the General Manager (Exh. 1 pg. 1) was also knowledgeable about day to day operations at the firm and often got the information that we requested, however, he was not usually the person who presented information to the team.

Mr. Qian Jiangen, Sr. Manager, Production (Exh.1 pg. 1) assisted in responding to questions that arose during the batch record reviews, process validations review and was present during all walk-through activities.

Mr. Wang Zhong, the head of Engineering (Exh. 1 pg. 1) assisted in responding to questions about equipment maintenance and operation.

Dr. Y. Wang provided a site map (Exh. 4 pg.1), which showed Changzhou Techpool shared two border lines with the current establishment; he stated that the two firms shared an employee cafeteria, only. The CZSPL property, in the lower left hand corner of Exhibit #4 pg. 1, had two buildings, designated 11 & 12 (not including the guard house); building 11 was for administrative activities and building 12 housed all warehousing, manufacturing, packaging and testing operations for all products (Exh. 4 pg. 2). He stated that the firm made Heparin Sodium USP, an API for the US market, called "1060", the name given to this site's purification process. Almost all 1060 was sold to SPL in the USA. Dr. Y. Wang stated that annually two or three lots of 1060 were sold back to Changzhou Techpool (CT) which was a major vendor of Heparin Crude to this firm. He stated that these lots were not sold to customers by CT.

CT was one of two "consolidator/processors" that supply Heparin Crude to the current establishment as raw material for the purification process, which results in Heparin Sodium USP (1060), CZSPL's largest volume product. In 2007, approximately 50 API batches were made. CZSPL also made two products in small quantities, both were made from the 1060 API; Heparin Lithium (sent to the USA, Japan and Denmark) and distributed into the Japanese and EU device markets and Dalteparin, a pharmaceutical, sent to SPL and distributed in Japan (Exh. 3). It was observed that GAG (see below), Heparin Lithium and Dalteparin had separate manufacturing areas from the 1060 processing rooms. According to Dr. Y. Wang and Mr. W. Ruan, Heparin Lithium, Heparin Sodium and Dalteparin all shared only one piece of equipment, the lyophilizer. A list of customers was provided (Exh. 3).

Sales charts were obtained (Exh. 5) and showed a product named GAG sent to SPL in the USA. Dr. Y. Wang stated that GAG stood for Glucosamine Glucan, a heparin process by-product, which was concentrated and dried from the from the three heparin processes. Later annual production report review identified GAGs as glucosaminoglycans (Exh. 52C pg. 8, 9). Notably, approximately five large foil bags, each containing ≥ 25kg of GAG, were observed stored behind a locker door labeled "non-GMP", on 2/20/08, in the finished product cage. The door to the GAG preparation room had a window and I observed a ~100 gallon mixing vessel in the room. Dr. Y. Wang had stated that Chondroiten Sulfates were also impurities removed during the processes; however, it was not reported to the team as a CZSPL "product". No records or either isolation or purification of Chondroiten Sulfates were observed or reviewed and, the sales records provided (Exh. 5) showed no Chondroiten shipments.

Dr. Y. Wang stated that CZSPL was responsible for procuring, sampling, testing (limited to the Polymerase Chain Reaction test (PCR)) and shipment of Heparin Crude to SPL for further manufacture. He stated that the PCR test results were attached to the CT Certificate of Analysis (CoA) received with the lot and then the material was shipped to SPL.

Changzhou Techpool Pharmaceutical Co. Ltd. (see EIR dated 2/28/08) (CT) and Hangzhou Ruihua Biochemical Co. Ltd. (see EIR dated 2/29/08) (HR)(address-Exh. 7) were the two currently approved consolidator/processors of Heparin Crude used in the 1060 process (Exh. 20 pg. 1-2, Exh. 21 pg 1-2). Both approved vendors processed crude heparin derived from CZSPL approved, audited workshops (lists-Exh. 16 & 17) into Heparin Crude, the raw material for the CZSPL 1060 process.

On 2/26/08 an FDA483 Inspectional Observations was issued to the General Manager, Dr. Y. Wang and discussed with Mr. X. He, Mr. W. Ruan in the presence of Mr. W. Chen and Mr. Bruce Ross. An inaccuracy in FDA483#5 was changed during the discussion with management. The discussion is addressed in the body of this report. Management stated that the items would be corrected and promised to respond in writing.

This report was written by CSO R. Brown, except for the Laboratory Controls Section, which was written by Chemist Z. Gu.

PRODUCT COVERAGE

The manufacturing process for Heparin Sodium USP, the API, is a purification process. Heparin was described as a hygroscopic powder, it is soluble in water (WFI used) and not very soluble in alcohol (used). It is made of polysaccharides and consists of material with a wide range of molecular weights. Heparin Crude is the starting material in the following, 1060, process at CZSPL for which a diagram was provided (Exh. 8)(current batch record-Exh. 37):

1. Heparin Crude is dissolved in water, the solution is made , and then)
2. The clarified solution is made , and then ( )
3. The solution is and is added. Reaction for to (
4. Approximately is added to heparin. ( )
5. The is is added and the solution made is added. is added. Reaction for . Then a , or , and the solution (; which are
6. A adjustment to , add , add , stir, add , stir, . Add approximately to the heparin ( ).
7. Add approximately to the heparin.
8. in , add , add approximately to the heparin . (The , steps 6, 7 & 8 (above), Dr. Y. Wang stated were for removal of impurities including non-heparin polysaccharides, with no anti-coagulant activity, such as Chondroiten Sulfates which came in three forms, A, B and C. He stated that the high molecular weight entities removed during the process were the Chondroiten Sulfates, some Heparin and GAG, which he called Glucosamine Glucan, which he identified as a heparin by-product. Chondroiten Sulfate Form B, he said, was Dermatin Sulfate. He stated that these impurities also included low molecular weight entities. Dr. Y. Wang stated that non-polysaccharides were also removed and that these included proteins, nucleotides, bacteria and virus.)
9. in water, make , add to (add if necessary). (;)
10. in to a specific
11. (USDA viral inactivation certificate (-Exh. 62)
12. Mill the powder
13. Package into double bags into a foil bag. Place in a plastic drum.

Dr. Y. Wang orally described the impurities removed in the steps of the process to the team and they are included in the above process description as the information in parentheses.

The first tour of the manufacturing facility was on 2/20/08 and it included the warehouse areas, as well as Heparin manufacturing, including the packaging area. Tour of the laboratory was performed by CO Gu on a separate inspectional day. As we walked through the warehouse the forward and held raw materials on pallets on racks and in refrigerators, locked cabinets with retained API lots and the stability storage chambers.

On 2/21/08, it was noted that a partial container, a plastic jug, of , returned from production, was in a refrigerator/freezer. The warehouse manager, Mr. Dean Liu, stated (translated) that he waited for production to return any partial container and that they only had the containers for a few minutes (see FDA483 #8). The raw material inventory receipt log (e.g. Exh. 13) was checked and showed the lot had been received. The raw material inventory card (e.g. Exh. 29-for Heparin Crude lots received) for the lot was checked and did not indicate any returns from production by amount or the condition of the returned material. It was pointed out that the only record of a container from the lot having been returned was the stick-on label on the particular plastic jug where a weight was handwritten onto the margins of the label. The written procedure for receipt by the warehouse did not address productions' returns handling and records. Also, it was noted that some of the containers of the lot had a "Sampled" stick-on label. The raw material inventory record did not show the amount sampled removed on the inventory record and the written procedure (Exh. 61 pg. 4) did not require the record of removal be made. Dr. Y. Wang stated that the amounts of materials consumed were recorded on the batch records. I, CSO Brown pointed out that that alone was not enough to meet cGMP.

Heparin Crude, GAG and Heparin API were stored in the back of the warehouse area in a large locked cage which contained about twenty locked upper and lower lockers each marked as storage locations. Storage of approximately five ~25 kg bags of GAG was observed in a locker labeled non-GMP. Sealed drums of an unreleased lot, the result of an OOT low potency batch that was re-processed and found to be OOT for (Exh. 58)), lot 1060-07-0019 (CR#459760, Exh. 33) were on the floor in the middle of the cage. On 2/24/08 one of the drums was opened and contained a large unlabeled foil bag (FDA 483 #10). Only the drum lid had been labeled; it had stick-on yellow and green quarantine/release labels and a sample label. Review showed that the unlabeled foil bag was current practice (e.g. Exh. 37 pg. 51-53) and the labeling on drum lids only was current practice. The unlabeled bags in drums with the lids only labeled were pointed out as inadequate to secure the identity of the material inside. The firm reported that they had one customer for the API; the option to not label the foil bags appeared to be also unnecessary.

(also see FDA483#7-for discussion of PE containers used as in-process equipment; thier lack of cleanliness and the "cleaned" tag practice)

It was noted that the firm had two small in the crude processing room; they were about 3.5 feet high. The Production Manager stated that they were both used: one was used in operation while sludge was being removed from the other. A Production employee demonstrated how the sludge would be removed; he brought a unit over to the cleaning room and put it on the table and unscrewed the top. In the same room, steel wool was observed stored in a cabinet. The Production Manager responded that the steel wool was used to clean the sink and the stainless steel table only. He stated that it was not included in the written SOP (Exh. 57). It was pointed out that steel wool was not appropriate in a pharmaceutical manufacturing environment because pieces might break off of it.

The Production Manager explained that after the first 50 liters of the mixture was the was replaced and checked for the thickness of the sludge inside. It was used to estimate how many liters the could handle until a switch was necessary. The risk to the product solution introduced by the repeated changing of and by the manual sludge removal process itself has not been evaluated. The practice of switching was not described in the written operating procedure (Exh. 49). Batch record review showed that activities (Exh. 37 pg. after -pg. 10, after -pg. 11, afte reaction-pg. 22) lasted for hours. The risk posed to the purity of the product, in solution for duration of the steps, has not been evaluated (see FDA483 #3).

Validation of the manufacturing process occurred initially in 2003 and again in 2005 (and is addressed in FDA483#1-2 section of this EIR).

(Reprocessing comments are included in the Quality System section of this EIR)

MANUFACTURER'S LOT CODE

API lot numbers appeared as follows: 1060-07-0009
The 1060 was the name of the process and identified the product. The "07" designated the year the product was manufactured. The "0009" would be the ninth batch from process manufactured in the calendar year

COMPLAINTS

There were no complaints that had been received by the firm.

QUALITY SYSTEM

Review of the annual production reviews (APRs) (2004, 1/05-5/06 and 6/06-5/07 (Exh. 52C, Exh. 52B and Exh 52A) for Heparin Sodium USP was performed. For the same time period, lists of deviations (Exh. 59), Lab Investigation Report situations (out of trend (OOT) and out of specification (OOS)) (Exh. 58) and Quality Observations (Exh. 60) were reviewed and investigations selected for review. Review of investigations showed that there was the science to back up findings was lacking, reprocessing from the last step was the normal corrective action taken. Preventative action was not identified in the investigations because the reasons for the failures were not identified. There were no returned products or previously recalled products.

Review of the APRs showed that re-processing was performed on some OOT API lots and on all OOS API lots, less than a handful of events per year. In general (Exh. 45 & 46C), reprocessing began with the final [redacted] or [redacted] step (Step 8 in the Product Coverage Process list). Also after the "final [redacted], there were 2 [redacted] by addition of [redacted] a [redacted] adjustment then freeze drying. It was noted that two reprocessed batches were discussed in the 2007 APR which (Exh. 52B pg. 10) had resulted in different yield percentages and the discussion showed that if the [redacted] happened in [redacted], which was closest to [redacted], the lowest percent used, the [redacted] resulted in a low yield. The 2006 APR also concluded that heparin was sensitive to alcohol concentration. In addition, discussion in the 2006 APR revealed that an "old" process (before re-validation approved 1/05) lot, #1060-05-0013 had resulted in an unexpectedly low yield. The GAGs for the lot were collected and weighed for the batch and, calculation showed that 16% of the heparin had not [redacted] out and had been isolated along with the GAGs. If the GAGs were added to the heparin yield (68%) then a "normal" amount of heparin had actually been available (Exh. 52B pg. 11).

Dr. Y. Wang, the General Manager, stated that he was the most responsible person at the establishment. He also stated that he was not involved in the day to day activities of the Production Department or of the Quality Assurance Department. He expressed confidence in Mr. W. Ruan and explained that he was attending an intense monthly course in cGMP, training given in Beijing. The Quality Unit consisted of 4 persons in addition to Mr. W. Ruan, the Manager. Mr. X. Ruan stated that he had daily meetings with the Production Department. Mr. W. Ruan stated that the successful cleaning validation that had been accomplished recently for the lyophilizer had been of great interest to him. Cleaning operations for heparin manufacturing areas and equipment involved water and ethanol (see lyophilization cleaning procedure (Exh. 51). Training records for persons who operated the lyophilizer were reviewed.

In regards to the ongoing Baxter recall, this firm had an open investigation and had conducted a traceback of about half of the API lots made in 2007 and sold to the USA to the workshop level (Exh. 43). For each finished product lot, the raw material Crude Heparin lot numbers appear next to two potency values, the CZSPL potency, listed first (and used as the Batch Record calculation potency values) followed by the supplier potency value. For items in the second group (not yet recalled-when this inspection began), it was noted that for several raw material lots, the vendor potency was ~ 3% higher than the CZSPL value.

0709005 ~250
0709039 ~250
0709040 ~200
0709041 ~400
0709043 ~250
0709044 ~250

RAW MATERIALS/VENDOR QUALIFICATION

A list of raw material suppliers was provided (Exh. 10). Mr. W. Ruan stated that the I supplier, Kunshan Jingcheng, had not changed- and, review of approved "Documentation Change" requests for going back to 2002 verified this. Some of the raw materials listed were also used in manufacture of the Dalteparin and Heparin Lithium; the solid NaOH and concentrated HCl.

According to Dr. Y. Wang, vendors CT and HR purified (cruder) heparin into Heparin Crude that met the CZSPL quality requirements (Exh. 11). The CoAs (e.g. Exh 76 pg. 6, Exh. 31) from the suppliers were CZSPLs only assurance that the Heparin Crude received was from porcine intestine.

Dr. Y. Wang stated that previous to the 9/10/07 approval of Hangzhou Ruihua, only the CT Heparin Crude receivals were used to make Heparin Sodium USP at this facility. He stated that there was one error (FDA483 #6) and that several lots of Heparin Crude, lots CSP-609053, CSP-609054 and CSP-609055 (verified by Exh. 25) were received 7-8/06 (Exh. 13 pg. 25, 26) and used in API lots 1060-06-0035, 1060-06-0036 and 1060-06-0037 (see Exh. 76). Review of the Blend Record, a record that CT (and HR) kept about the source workshops, was performed (e.g. Exh. 32 for HR Blend Record in Chinese). Notably, lot #1060-06-0035 was OOT low assay, was reworked into lot 1060-060051 (Exh. 45), and that is a lot which was sold to SPL, along with, also lot 1060-07-0037 (Exh. 63).

Dr. Y. Wang stated at first, that the Blend Records were, since vendor re-qualification, received with the Heparin Crude Certificate of Analysis (CoA). It was later discovered that this was not the case, that the blend records used to traceback the (initially) recalled lots as well as some other USA marketed lots (Exh. 43), and available for our review, were only provided by CT upon request. Dr. Y. Wang stated that prior to 3/06, CT did not have records adequate for a traceback to the workshops. He also stated that HR had records traceable back to the workshops since 9/07.

Mr. W. Ruan stated that there were workshops that had been eliminated as sources during the 2005 heparin vendor audit process and provided a list of Techpool workshops that had been rejected (Exh. 18-first names were Hejiang, MianYan, Yanchen & Shandong) in 2005; when Mr. X. He, Asst. to the GM, had performed the audits. Mr. X. He audited Heijiang 10/05 and they were disqualified from use (FDA483 #6).

Vendor re-qualification of CT and it's workshops was approved 9/10/07 (Exh. 20 pg. 1). Vendor qualification of HR and it's workshops was also approved on 9/10/07 (Exh. 21 pg. 1). The workshop process was described in short (see Exh.20 pg. 115) as adding enzyme to the mucosa in a basic, salt solution, filter, add resin. The heparin adsorbs onto the resin, then it was eluted from the resin with a high salt concentration solution and the heparin precipitated with ethanol. The precipitate was dried.

Mr. W. Ruan performed the audits associated with the 2007 vendor qualifications along with a CT representative. A translation of the audit questions was obtained (Exh. 19).

According to Mr. W. Ruan, CT and 12 (Exh. 20 pg. 13, Exh.16) source workshops, were individually visited (1st page of individual workshop reports- Exh. 20 pg. 15, 28, 34, 43, 50, 59, 68, 80, 85, 94, 104 & 113). The reports are in Chinese. Mr. W. Ruan stated that they described conditions revealed in the firms' responses to audit questions and observations during the visit. Photographs of the workshops were included in the reports. Mr. W. Ruan stated that the workshop audits began in 7/07; and that any handwritten notes had been thrown away when the information was typewritten. He stated that the workshops were required to have written records of their sources and written records of their own processing activities. The workshops were required to use the same process as described in the vendor qualification (VQ) report. He stated that deviant workshop process material was evaluated here at SPL, by bench scale purification, and stability studies. The CT purification process was also described (Exh. 20 pg. 115); it involved solubilizing heparin in salt water and precipitating it out of solution with alcohol and drying at 90-100°C, milling and blending. There was a 2006 written procedure designed specifically for qualifying the heparin crude vendors (Exh. 15, compare to general procedure (Exh. 14)).

The new vendor qualification (VQ) report was also reviewed for the Heparin Crude from HR. Thirteen workshops were also audited and approved (Exh. 21 pg. 1)(Exh. 17 pg. 1-2) and in 9/07 the HR Heparin Crude became available for use in the CZSPL "1060" process. Notably, one of the Workshops is named Hangzhou Ruihua Qingpu and is located in Shanghai. The VQ included workshop photographs and responses to the audit; it appeared to have been done in the same manner as the CT VQ. Previous to the 9/10/2007, CZSPL purchased Heparin Crude from HR. It was all sent to SPL for further manufacture by the SPL 1035 process, into Heparin Sodium USP and was not used in the CZSPL 1060 purification process. Review of the sales chart (Exh. 5) showed that historically, most but not all, Heparin Crude shipped to SPL was from HR.

Full testing of Heparin Crude intended for the 1060 process was done on every received lot. The tests were (Exh. 11):

Appearance
Heparin ID test (for Sodium)
Potency by the USP monograph test method (NLT USP units/mg)
LOD
pH
Protein (a turbidity test)

Reportedly, the above tests were all performed using the USP test methods. Other standard information secured for these lots was:

UV Absorbance @ 260 and 280 (for information only)
Vendor CoA
Vendor label as porcine, heparin, with a lot number

Mr. Wang stated that since 6/07, every incoming lot of Heparin Crude had been tested by Polymerase Chain Reaction (PCR) for source species verification. The PCR test was not included on the current Heparin Crude specification. Mr. W. Ruan stated that they had not gotten around to changing the specification, but that it was being performed. Review of a spreadsheet (Exh. 24) listing the batches to date that received PCR testing and comparison of it to the warehouse receipt log in 2007, showed that all lots received since 7/07 had been PCR tested, except for some very recent receivals.

Notably, the person who was responsible for performing the PCR test was not available for interview until 2/25/08.

In response to an inquiry into potency cross outs in the warehouse receival log for heparin crude receipts between 6/26 and 7/4/07 (Exh. 13 pg. 12 & 13), Dr. Y. Wang stated that sometimes the assay value for an incoming lot might have been changed because the CZSPL potency test had differed by more than 2.5% from the CT CoA potency value. He stated that there was a negotiation that started and that CT would usually retest the material and issue a new CoA. The raw material files for two lots CSP-709032 & CSP-709033 were checked and they contained only one CoA. No explanation was provided.

Cursory review of the Warehouse Receipt Logs showed that Heparin Crude receivals from CT have outpaced receivals from HR by almost 2 to 1, starting in 2006. It was noted that on occasion, Heparin Crude from other suppliers were received in small amounts. Follow up showed that they were shipments from potential new suppliers that were determined to be not acceptable. In only one case was a Heparin crude lot observed received anew (after having been returned) and it received an "R" designation after the CT lot number, CSP-0709046R, and was received in more than one portion (Exh. 13 pg. 8-10). The reason for the return had been financial, according to Dr. Y. Wang; there was no written deviation or investigation into the matter.

Post inspection review of the Warehouse Receipt Logs also showed that some Heparin Crude lots were received out of order. The delayed (non-sequential order) lots in 2006 were CSP-609012, 020, 027, 030, 033, 034, 047, 049 & 050. None of the delayed lots happened to have been incorporated into sampled API lots. In 2007, there was only one delayed lot CSP-709062. There were also "missing" CT lot numbers in 2006 that were never received: these were CSP-609005, 006, 008, 037, 040, 041, 042, 043, 045, 069, 076, 081, 085, 093 & 094. In 2007 there was one missing Techpool lot number, CSP-709004. A list of lots with the associated raw materials was also provided (Exh. 25) which showed the raw material lots associated with all finished products lots made from 2004 through the end of 2007.

Review of a traceback (Exh. 43) provided for about half of the 2007 1060 lots sold to SPL, showed, consistently, CZSPL potency totals that were higher than the CT (vendor) potency value. Potency was measured in Units/mg for both raw material and finished product. The units of heparin on the traceback were described as total mega units of Heparin available for manufacture into the USP grade material, one million units. This traceback (Exh. 43) also showed that CZSPL incorporated tailings into two batches; 135 MMU (an MMU is one million Units of Heparin Sodium USP)of 15501MMU (total raw material input, 0.8%) in Heparin Sodium USP lot #1060-07-002 and 57MMU in 14604MMU (total raw material input, 0.39%) in lot # 1060-07-0038. These tailings were described as small portions of Heparin Crude leftover in the bottom of the poly bags received.

We observed raw material Heparin Crude in locked cages in the warehouse. The CT Heparin Crude was a shade lighter than the HR Heparin Crude and noticeably less dense.

SAMPLES

On 2/21/08 and on 2/25/08 samples of finished product lots were collected (Collection Reports #459750 through #459777).

Of note:
CR#459753 for lot 1060-06-0051 was reprocessed from 1060-06-0035 an atypical low potency batch (Exh. 45). Reprocessing (from 1060-07-0035-OOT low potency (Exh. 45 pg. 1)) was performed 12/06 and the batch released 1/07. The re-processing used slightly more hot WFI (by 10%) during resuspension (Exh. 45 pg. 10) with no deviation report. Shipping documents were collected (Exh. 63).

CR# 459760 lot 1060-07-0019 that was OOT low potency reprocessed low potency (again) batch made with raw material from HR Heparin Crude raw material lots C20070314 and C20070315 (Exh. 29, 32 & 33) that went into a batch that failed and was reprocessed.

Several samples of API lots were collected that had not been sent to SPL, in the USA (see Exh. 5), these were CR#459754, lot 1060-07-0013 and CR#459757 lot 1060-07-0051 and CR#459760 for lot 1060-07-0019, an OOT low potency batch (Exh. 60).

LABORATORY CONTROL SYSTEM (ZQG):

The area occupied by the quality control laboratory in CZSPL was about 3,000 square feet and included a microbiology preparation room, a polymerase chain reaction (PCR) sample preparation room, an instrument room, and general chemistry area. There were a total of 7 analysts in the QC lab including the QC manager. The manager of the QC lab was Mr. Mao Xingchang who provided most of the laboratory information.

The QC laboratory's responsibility included testing of raw materials, final product (API) release, and stability studies. Tests on purified water (PW) and water for injection (WFI) were also conducted in the QC laboratory, such as total organic carbon (TOC), conductivity, endotoxin and microbial limit tests.

The QC laboratory was equipped with necessary instruments to allow the performance of all tests on the API, Heparin sodium USP, as follows:

	Instrument	Maker or Model	Purpose
1	Thermal Cyclar	Eppendorf	PCR test to confirm porcine source for crude heparin
2	TOC Analyzer	Shimadzu TOC-V CSH	PW and WFI testing
3	Digital Flame Analyzer	Model 2655-00	Sodium identity test
4	YB-2 Vacuum Dryer		Loss on drying test
5			API test
6	HPLC	Agilent 1200 Series	Use in development, not for Heparin sodium, USP test
7	Dual Wavelength Flying Spot Scanning Densitomer	Shimadzu CS-9301PC	Use for development study, not for Heparin sodium, USP test
8	UV-Visible spectrophotometer	Shimadzu UV-2550	Absorbance test on Heparin
9	Gel Logic 200 Imagine System		UV photo for PCR test
10	GC	SRI 8610 C	For residual solvent test
11	Stability Chamber	Caron 6030	Stability study

The glassware used in QC lab for analytical work was grade A glassware. It was properly cleaned and stored. Reagent bottles were properly labeled with date when opened or prepared, and expiration date. Instrument use was recorded in use log books and included the batch numbers of the samples tested. Original data and documents were properly stored. All balances were calibrated with an external standard weight before each use. The calibrations are recorded in the balance use log books.

The QC laboratory's instrument use logs, instrument maintenance and calibration records including some IQ/OQ/PQ records, USP standard receiving and use records, and sample analysis reports were audited against the relevant procedures and raw data.

The firm's stability study program (SOP CZ-50-0012, effective date of Sept 10, 2007) has been reviewed. The stability program included accelerated and long term stability conditions. The stability program required that at least one batch per year per product should be added to the stability program. The stability studies were conducted based on ICH guidelines under the following conditions and time periods:

- Long term at 25°C/60% RH; initial, 3, 6, 9, 12, 18, and 24 month
- Accelerated at 40°C/75% RH; initial, 1, 2, 3, and 6 month

Two stability chamber Model CARON 6030 were used to store heparin stability samples (for long term and accelerated conditions, respectively). The stability chambers were equipped with a continuous temperature and humidity recorder. The heat distribution study for the chambers was performed by a Government Agency once a year. Calibration of temperature and humidity controller and the recorder were performed. The calibration schedules and results were reviewed during the inspection.

Stability tables that included all studies performed was provided (Exh. 74). A selected number of long term stability test results and raw data for various batches were reviewed during the inspection. No trend or deviations were observed regarding appearance, potency, pH, LOD and microbial limit (USP monograph specifications). The results were within the acceptance limits.

Polymerase Chain Reaction

There was a dedicated room with two hoods for conducting polymerase chain reaction (PCR) on crude heparin materials to identify and/or confirm the source of the crude material. One hood was used for the preparation of DNA samples and the other hood was used for preparation of non-DNA samples in order to prevent cross-contamination. The PCR method was originally developed by Aventis Pharma (France). It was transferred to CZSPL by SPL personnel. The tech-transfer and/or suitability study for the PCR test was conducted to demonstrate that the method was suitable for the actual condition of use at CZSPL. The test methods were reviewed. The study included:

1) Amplification of DNA which is isolated from the crude material in order to obtain enough DNA for run gel electrophoresis experiment.

2) Visual detection by conducting gel electrophoresis to separate DNA on gel based on size of the DNA segments against standards (porcine, bovine, goat and sheep).
3) Verify the species by using restriction enzymes to digest the amplified product to provide specific pattern to further confirm the results.

Standards

USP standards of Heparin Sodium (Lot K-5), sucrose (Lot HIC223), 1,4-benzoquinone (Lot-G1B145), and Endotoxin (Lot G3E069, 10,000 SP unit per vial) were purchased and used as primary reference standards. The Heparin Sodium, USP reference standard use log book, was begun in 2002 and was reviewed with no objectionable conditions observed. Twenty ampoules of the current batch were in stock during this inspection and they will be expired on June 2008.

The SOP "Quality Control Laboratory Reagent and Analytical Reference Standards" (CZ-50-0010, effective date is Sept. 1, 2006) was reviewed; it described the procedures for receiving, standardizing, and storing reference standards, etc.

The SOP "Standardization of 1,4-Benzoquinone and Sucrose Using USP Reference Standard" (CZ-70-0026) and a report on standardization results have been reviewed and it appears adequate. The standardization has an acceptable limit of RSD ≤2% by comparison with standard curve on TOC analysis within 98% - 102% at 30 ppm concentration (50, 40, 30, 20 and 10 ppm points, each point with six replicate).

Microbiology

There was a separate room (RM 305) in QC laboratory used for microbiology. The room was monitored at Class 100,000 and was equipped with a laminar flow hood for local Class 100, used for the preparation of samples. There were three microbiology lab incubators and two analysts were responsible for conducting all microbiology testing.

The autoclave used for sterilization of culture media was qualified in 2002. The Installation/Operational Qualification report (IOQ-00-0004) and Performance Qualification reports (PQ-01-0067) for the autoclave were reviewed. The temperature detector and pressure gauge of the autoclave were regularly calibrated. A biological indicator was routinely placed inside each autoclave load.

Water System

CZSPL's water system was built and qualified in 2001. The report "Performance Qualification for the Purified Water (PW) and Water for Injection (WFI) System" was reviewed; during the water system qualification, PW/WFI was tested five days a week for 30 days. Then, an abbreviated sampling plan was used for testing for 11 months. PW/WFI was tested according to current USP monograph standard. There was no OOS observed during validation period.

The water testing results were reviewed from 2004 through 2008. WFI was tested for conductivity, pH, TOC, microbial limit and endotoxin limit. The current monitoring program required testing of each use point for PW once a week and testing of each WFI use point twice a week.

Assignment Responses:
Production System Assignment

1.a) The firm does maintain production batch records and packaging records. They are called manufacturing instruction (MI) (e.g. Exh. 37).

b) Each incoming lot of Heparin Crude that is to be used in the 1060 process is tested for all criteria discussed in this report (see Raw Materials/Vendor Qualification section of this report). For incoming lots that are to be sent to SPL for 1035 processing, the drums are sampled and a PCR test only is performed.

c) Mr. Y. Wang stated that waste protein was removed at the and processing steps in the beginning of the manufacturing process. Mr. Y. Wang stated that there was no information to show that the process would remove histamine.

d) Review of 2007 batch records showed that the process changes were made according to the latest, 1/05, process validation exercise conclusions that are discussed in this report (FDA483#1&2). This inspection found that the batch records were not adequately specific (FDA483#3). This inspection found that critical control points for the purification process were not defined (FDA483#1). Suitability of some of the processing equipment, polyethylene tanks, and the lyophilizer records were determined to be deficient during this inspection (see FDA483#7 & #3). Major deviations were reviewed; for the list of process deviation investigations (see Exh. 59); the Quality Unit was cited (FDA483#5) for conducting investigations and concluding them without coming up with preventative action (FDA483#5). Yields were performed only at the conclusion of each API batch; intermediate steps that necessitated calculations related to amount of "available" raw material, were done using the CZSPL total potency units. A lack of time limits for precipitation steps, and, importantly, the lack of criteria in the batch records for using the full value of time ranges permitted by the batch record was discussed as part of FDA483#3. No comparison has been made to the application.

e) In process testing for alcohol amount and for pH was performed. These tests were used to verify that the process parameters were achieved. Interim values were not observed recorded on the batch record (FDA483#3). These in process tests and measurements were not designed to indicate the completion of a step from a purification achievement perspective (see FDA483#1). There was no justification given by firm management for the lack of in process tests that would indicate changes in purity; the most recent process validation appeared to have been accomplished to facilitate the purchase of Heparin Crude.

Laboratory System

a) This firm did not perform testing for peptides, nucleic acids, histamine or other impurities such as heparin by products or heparin degradation products. The protein test in the USP was performed on Heparin Crude and on the Heparin API and the lack of verification for the test method was cited (FDA483#4).

b) The firm did not have an impurity profile (see FDA483#2) for Heparin Sodium USP. Dr. Y. Wang stated that there was no written procedure addressing the investigation and handling of unusual impurities.

c) The specifications and impurities addressed by the API specifications are not adequate to indicate the presence of impurity (see FDA483#2); the firm performs USP testing for *protein*, nitrogen determination, *heavy metals* and total aerobic microbiological count; the underlined tests, above were cited as not adequately verified (FDA483#4) and the test methods for the tests in italics, above, were evaluated in FDA483#1 and shown to be inadequate measurements for the purpose for which they were intended, API release, raw material evaluation and during process validation.

d) A list of historical OOS; all OOSs were collected (Exh. 58) and many of the investigations were reviewed (e.g. Exh. 46B) and inadequate investigations were cited (FDA483#5). Low, OOT potency batches were covered as part of the firm's approach to reprocessing (see Quality System section of this report and FDA483#1).

e) The firm performs USP testing. The lack of method verification for the USP tests performed on the API was evaluated and was cited (see FDA483#4). Other laboratory controls were addressed in the Laboratory Control System section of this report.

Quality System

a) The firm had performed process validation and, inadequacies in the validations are discussed in FDA483#1&2. This inspection covered the early, 1/03 process validation, batches made just after pilot batches, and the re-validation. The characterization for Heparin Crude was incomplete, and has been addressed in FDA483#1&2). The effect of the manufacturing steps on potency and on purity, both indicators of the stability of the process, have not been fully evaluated and is discussed in FDA483#1&2 and also in the Quality System section of this report.

b) The firm does have a quality system and it tracks the quality of records associated with each batch and is responsible for release of the API. Annual production reviews (APR) are discussed in the Quality Systems section of this report and contain all trend information (there were no in-process control trends discussed in documents provided by the firm (also see Exh. 52). The APR were used to lookback, anew, at errors by QA. Change documents were provided during this inspection and have been included herein, as appropriate. The firm had historically, had no returned API. The firm had historically no complaints received. Changes to the process initiated as part of both the 1/03, 1/05 process validations are fully discussed in this report (FDA483#1&2). A list of deviations was provided (Exh. 59).

c) The firm has only used the USP protein method, a turbidity presence (or not) test, for protein evaluation. There were no test methods for detecting peptide or nucleic acid acid content of the

Heparin Crude established. The firm performed PCR testing on each incoming batch of Heparin Crude to establish the species from which the Heparin Crude was derived. All rejected product was noted on the OOS list obtained (Exh.58), according to Mr. W. Ruan and, it was observed that rejected product is frequently reworked from the third process forward. The firm has attempted evaluation of rework process as discussed in the Quality System section of this EIR. However, the concentration of in the , which the firm speculates in the APRs, affects potency, purity and yield, has not been fully evaluated as a part of a validation exercise. The vendor qualification program is discussed in the Raw Material/Vendor Qualification section of this report.

d) The vendor qualification program is fully discussed in the Raw Material/Vendor Qualification section of this report. Traceability back to the workshop was reportedly available at the Heparin Crude vendors; for CT, it was reportedly available for 3/06 and afterwards. For HR, it was reportedly available since 9/07. The firm maintained a CoA for each lot of Heparin Crude purchased; it was stated to the team that some CoAs may have been replacements for originally sent CoAs (see Raw Material/Vendor Qualification section of this report). The firm maintained a list of workshops that were determined to be not acceptable for vendor CT to use (Exh. 18). Mr. W. Ruan stated that they had never sent complaints sent to any Heparin Crude vendors. One instance of the re-receipt of a lot of Heparin Crude from CT was noted and Dr. Y. Wang stated that it was not reworked, there was a question about cost of the lot (see Raw Materials/Vendor Qualification section of this report).

e) The firm did not perform testing during stability program testing that would indicate heparin degradation products. Acceptable potency test results have been obtained and have been used, inappropriately (see FDA483#2), as support for the two year retest date. There were no stability failures observed (see all stability data-Exh. 74).

f) Staffing of the quality unit was considered to be adequate. There was no person with special knowledge of heparin at the firm to guide decisions made by the quality unit.

Facilities and Equipment System

a) Material flow in the manufacturing area was deficient and the deficient practice was not included in the written procedure (see FDA483#9). Dr. Y. Wang stated that Heparin has not sensitized any firm personnel. Substances that come into contact with the equipment (heating and cooling fluids for tanks) were reviewed and there were no objectionable findings. In the case of the PE tanks, the tank material itself as a potential added substance, and steel wool (stored and used on surfaces where in process cleaning takes place) were noted and brought to the attention of management. The PW and WFI systems (diagram Exh. 9) were reviewed during this inspection (see Laboratory Control System section of this report) and, qualification information was reviewed and determined to be acceptable. Maintenance and monitoring of the water system was reviewed. Cleaning validation procedures for the lyophilizer were made available for review; PE tank cleaning practices and procedures were discussed as part of FDA483#7. It was reported to the team that hot waters (PW and WFI) were used for cleaning in the Heparin manufacturing area, as well as 95% ethanol/water, only. During the inspection, it was ascertained that the calibration of PE tanks and small carboys, used to make up acid and base solutions used for production (and marked on the outer container sides in marker and in tape) was data that was not kept. There were no computer validations reviewed during this inspection.

Materials Systems

a) Packaging material in contact with the API was PE bags. Dr. Y. Wang stated that the bags were brought into the company from SPL and were the same bags as those used by SPL for the Heparin Sodium USP that was product of the 1035 process. Leachables data was requested and reportedly existed in Wisconsin. The data was not provided during the inspection (see FDA483#11).
b) The vendor qualification system for Heparin Crude is described in depth in the Raw Materials/Vendor Qualification section of this report. Heparin Crude was purchased against an agreed upon specification that included the names of the source workshops that could be used for the crude heparin. The written procedure that applied to vendors of materials other than the Heparin Crude was also reviewed (Exh. 14). The changes documentation for each supplier that has changed since 2004 was reviewed during this inspection. Notably, the supplier has not changed. The condition of that has been returned, partially used, from production to the warehouse was not recorded and this was cited as a deficiency (FDA483#8). This firm does not audit the vendors of other materials, according to Mr. W. Ruan. At least one lot of each "other" raw material was tested against the CZSPL specification annually, according to Mr. W. Ruan. There was no indication that "other" raw materials were purchased against an agreed upon specification. Raw material inventory recording deficiencies are noted in FDA483#8. The retest dates for raw materials were only on the container and, according to the Warehouse Manager it was his responsibility to have the raw materials retested before use. Lab slips with raw material sample test data for "other" materials; were not available to production as they manufactured goods, production relied upon the container label. The warehouse had a portable 10'X10' sampling tent.

REFUSALS

There were no refusals during this inspection.

ANNOTATED OBSERVATIONS:

1. There have been no critical processing steps identified for the Heparin Sodium USP purification process, and, the repeated and efficient removal of impurities, such as proteins, nucleotides, virus, endotoxin, bacteria and heavy metals at the appropriate, specified, process steps has not been evaluated. There was no report for annual HAP test results available.

The improvements offered by removal of a raw material absorbance test @260 & 280, a batch size increase an added tep, a change in pH for the tep and lyophilization solution concentration and parameter changes, approved in a 1/05 process validation report for Heparin Sodium USP, were not demonstrated.

---

2. There has been no impurity profile established for Heparin Sodium USP and no evaluation for degradants during stability program testing.

Dr. Y. Wang had described the impurities removed by the CZSPL process as (see Product Coverage section of this report) as protein, heavy metals, virus, nucleotides, bacteria, endotoxins, Chondroiten Sulfates, Glucosaminoglycans, and low molecular weight non-polysachharides (see the Product Coverage Process list in the Product Coverage section of this report-the parenthetical remarks).

Review of the 1/03 initial process validation for 1060 (Exh. 42A) showed that it defined a dissolution step, the step, the step, the step and the as the critical steps. Review of the initial Heparin 1060 process validation (Exh. 42A), approved 1/03, had acceptance criteria as follows: the step was to remove protein, and that and would be reduced to satisfy USP monograph requirements, along with a bioburden reduction to and decolorization was to be achieved and measured by an Absorbance values at Notably, absorbance at 260nm and 280nm were monitored. The firm ran three 1060 batches. The report showed that the validation exercise was approved.

Notably, the acceptance criteria did not associate the impurity removed at the specific steps with the step itself. Review of a batch record from 2004 (Exh. 35) showed that there was an step, however, it was not selected as a critical step. Dr. Y. Wang had stated that were reduced by the accomplishment of the step. In-process test samples were not removed after that step to show that the step in the process where the were actually reduced. In addition, there was no effort to identify or evaluate the , except using the USP test, a limit test.

According to Dr. Y. Wang, waste protein was removed at two steps; first at a step and secondly at the (critical) step. The in-process test results appear to have been based on the results of both steps; the effectiveness and efficiency of the critical step has not been measured. In addition, there has been no effort to validate the process of removal, the seven hours (e.g. Exh. 35 pg. 11) that it took to he solution.

The endotoxin reduction was claimed as happening at two critical steps: the step and the step. Each of these steps involved a reaction time, for hours at C (e.g. Exh. 35 pg. 17), and for the step, minutes reaction time with a slow (the caution is not defined) addition of (e.g. Exh. 35 pg. 23), to quench the reaction. The 3-6 hour reaction time was not challenged during the validation, and neither was the time it takes to quench the step. Notably there were in-process samples taken after each step-the post mixture was and put through a filter press-the post mixture was pH adjusted and was added to the heparin. There was no scientific reason proposed to indicate that endotoxins were destroyed or removed by either the reactions themselves, or the post-reaction work-ups. In addition, the sampling method used does not eliminate the possibility that the and steps may also have changed the endotoxin amounts.

The ability of the process to remove bacteria is associated in the validation report to the and the steps. The basis for the removal of bacterial contamination in these steps is not clear. The (0.1μ) filtration (e.g. Exh. 35 pg. 31 & 32) took place as part of the final step, also a critical step, but it comes after the and the steps. In addition, the bacterial evaluation (Exh. 42A pg. 5) failed to examine the types of contamination that might be expected to be normal in the Heparin Crude raw material.

Notably, viral inactivation and removal was not addressed in either this, the initial 1/03 process validation, nor in the newer 1/05 process validation. Three short reports about viral inactivation and removal were reviewed during this inspection (Exh. 22, 23E, 23F). The process comparison (Exh. 22) proposed that that the viral studies performed in 2002 (Exh. 23A, B & C), 1998 and 1997, be applied to the 1060 process. Ms. D. Kwiatkowski stated that the CZSPL material had never been used in the actual viral inactivation/removal studies. Exh. 22 showed that the processes 1035, 1037 and 1060 were the same except for the source material. Dr. Y. Wang stated that none of the model viruses used selected for use in the studies had mimicked the PRRS virus. PRRS reportedly cause Pig Blue Ear syndrome that killed hundreds of thousands of animals in mid-2007 in several Chinese Provinces. The report made clear that 3 steps were critical for viral inactivation: the step, the for hr and the hour step. Of Note, at CZSPL, the current manufacturing instruction shows the time range of hours (Exh. 37) and the step time range as min. (Exh. 37). Timed sample intervals of spiked materials were used to determine viral deactivation. When I asked Dr. Y. Wang if these steps were the critical processing steps for the CZSPL manufacturing process, he stated that they were not the critical steps.

As far as nucleotides as impurity is concerned, no DNA tests have been done on finished product at CZSPL, according to Dr. Y. Wang, he stated that nucleotides should not be present.

The 1/03 process validation failed to establish assurance that the purification steps accomplish what they were purported to achieve.

The second process validation study performed (Exh. 42C) was approved 1/05. The protocol (Exh. 42B) showed that the customer imposed Absorbance criteria @260 ( ) and @280 ( ) was to be eliminated. Changes to the manufacturing instruction (MI) were also part of the validation exercise, they were:

-Batch size increase (to of Heparin Crude)
-change to after addition
-added an step
-specified heparin concentration for lyophilization solution preparation

-new freeze dryer parameters

The MI change control document (Exh. 42D) showed the reasons for the changes and stated that the added step was to reduce impurities. Dr. Y. Wang stated that the and that the conditions of the were better at , but he stated that the firm had no data to show that this adjustment to the process was as efficient or as effective as the old process. Dr. Y. Wang stated that the remained behind in the solution and that the removed them away from the heparin.

The change control document (Exh. 42D) also stated that, without the Absorbance criteria, the Crude Heparin would be easier to "get".

The acceptance criteria were the same as those for the previous 1/03 process validation (Exh. 42B pg. 7), with a yield criteria added. The in-process sampling was added at the new step and the first were also sampled. The in-process testing done newly included an Absorbance value at . Dr. Y. Wang stated, and the protocol (Exh. 42B) showed, that there were no critical steps identified for process validation purposes. The protocol stated also (Exh. 42B pg. 6) that the CZSPL Test methods are USP test methods and would be used for the analyses.

The process validation report (Exh. 42C) summarized activities around the manufacture and testing of three Heparin Sodium USP batches 1060-04-0007, 1060-04-0008 and 1060-04-0009. Mr. W. Ruan stated that the lots were reportedly sent to market when the 3 months accelerated stability test results were determined to be acceptable.

For the protein reduction, decoloration, endotoxin and bioburden conclusions drawn by the 1/05 process validation (Exh. 42C pg. 6-7), the inadequacies of the data collection are the same as those expressed above, for the 1/03 process validation effort. Notably, the conclusion drawn was surprising in that it showed that they were gone after the step, contrary to the step purpose information that we had received from Dr. Y. Wang.

On 2/20/08, Dr. Y. Wang stated Absorbance at 260nm indicated the amount of nucleotides and that Absorbance at 280nm indicated the amount of protein and that the test had come out of the European Pharmacopeia. On 2/21/08, he stated that he had been mistaken and the absorbance at 260 indicated the amount of protein and the absorbance at 280 indicated the amount of nucleotides in the raw material. For the API, Dr. Y. Wang stated that he did not know what the measurement for a customer at was actually for. He stated that the Absorbance test was not done on finished API because it had no protein or nucleotides in it. It was noted that there was no absorbance test done on the API in the stability program (Exh. 74).

The table below shows that for the API lots sampled, the raw material lot absorbance values at 260nm in 2006 and 2007 (examples-Exh.79) for Heparin Crude would not meet the 1/05 obsoleted criteria of ( ) (Exh. 42B pg. 2). At the bottom of the table are the raw material Absorbances at 260nm and values for raw material, Heparin Crude lots used in the 1/05 validation (Exh. 42C), shown by receiving number only (Exh. 42C pg. 8). The table shows that the for the 1/05 process validation raw material quality, the absorbance values at 260nm, even though they were a little above the obsoleted specification, were not representative of the raw material, the Heparin Crude, that was currently considered acceptable with absorbance values of almost the norm. Also of note: the HR CoAs (Exh. 31) show a criteria for absorbance at 260 of and no information about absorbance at 280nm.

CR Number	API batch Number	Raw Material Lot	Rounded Abs@260	Raw Material Lot	Rounded Abs@260	Raw Material Lot	Rounded Abs@260
459750	1060-05-0030	CSP-509060	0.6	CSP-509059	0.9		
459751	1060-07-0007	CSP-609101	1.2	CSP-609100	1.6	CSP-609099	1.6
459752	1060-06-0038	CSP-609058	2	CSP-609059	1.3		
459753	1060-06-0051	CSP-609053	1.1	CSP-609054	1	CSP-609055	1
459754	1060-07-0013	CSP-709008	1.7	CSP-709009	1.2		
459755	1060-07-0029	CSP-709034	1.2	CSP-709035	1.1		
459756	1080-07-0028	CSP-709031	1.4	CSP-709032	1.4	CSP-709033	1.2
459757	1060-07-0051	CSP-709063	1.6	CSP-709064	1.6		
459758	1060-07-0006	CSP-709098	1.5	CSP-709099	1.6		
459759	1060-07-0044	CSP-709046R	0.6	CSP-709049	1.4	CSP-709050	1.4
459760	1060-07-0019	C20070314	1	C20070315	1.4		
459761	1060-07-0027	CSP-709029	1.3	CSP-709030	1.4	CSP-709031	1.4
459762	1060-07-0030	CSP-709035	1.1	CSP-709036	1.2	CSP-709037	1.1
459763	1060-04-0005	CSP-409030	0.9	CSP-409032	0.7		
459764	1060-07-0017	CSP-709013	1.5	CSP-709014	1.8	CSP709015	1.4
459765	1060-07-0018	CSP-709015	1.4	CSP-709016	1.4		
459766	1060-07-0015	CSP-709010	1.8	CSP-709011	1.8	CSP-709012	1.9
459767	1060-07-0026	CSP-709028	1	CSP-709029	1.3		
459768	1060-07-0014	CSP-709007	1.5	CSP-709010	1.8		
459769	1060-07-0023	CSP-709021	1.1	CSP-709024	0.6	CSP-709025	1.2
459770	1060-07-0002	CSP-709086	1.7	CSP-709087	1.9		
459771	1060-07-0022	CSP-709019	1.3	CSP-709020	0.9	CSP-709021	1.1
459772	1060-07-0009	CSP-709001	1.2	CSP-709002	1.3		
459773	1060-07-0025	CSP-709026	1.1	CSP-709027	1	CSP-709028	1
459774	1060-06-0030	CSP-609046	1.6	CSP-609048	0.6		
459775	1060-06-0042	CSP-609064	1.6	CSP-609065	1.6	CSP-609066	1.4
459776	1060-06-0046	CSP-609071	1.2	CSP-609072	1.3	CSP-609073	1
459777	1060-06-0049	CSP-609077	1.9	CSP-609080	1.6	CSP-609082	1.1
1/05 val	1060-04-0007	RN04100022	1.2	RN04100023	1.2		
1/05 val	1060-04-0008	RN04100023	1.2	RN0410024	1		

1/05 val	1060-04-0009	RN04100024	1	RN04100025	1.1

It appeared that the components contributing to the Absorbance at 260nm were in higher amounts than in the raw material procured and used in production before the 1/05 validation. The higher Absorbance at 260, if indicative of higher amounts of protein in the raw material, might also translate to the manufacturing process and the ability of the process to remove the added protein and other crude heparin components that might be associated with it.

The new (Exh. 75 pg. 1) and old (Exh. 75 pg.2-3) lyophilization equipment settings and parameters were collected and they were discussed with the Manager of Production and the Engineer, Mr. Wang Zhong. It appeared that the majority of removal of water was at °C in the new process. Data review showed that the old cycle left more residual alcohol on the powder (Exh. 75 pg. 4). Mr. W. Zhong stated that the operator had to go to the back of the lyophilizer to enter the next sequential step into the lyophilizer control panel. He stated that there was no software which recorded the settings or the settings changes. They were entered manually and there was no record of what was entered (see FDA483 #3). It was noted that each batch record reviewed contained a chart showing the recorded time/temperature/vacuum measurements made during lyophilization. Notably, there was no change to the unusual heating step at the end of the lyophilization, designed to hold the powder at °C for a hour minimum time (USDA certificate-Exh. 62).

The lyophilization part of the process underwent performance qualification for the use of different temperature and time ramp components. Dr. Y. Wang stated that he did not know why the concentration of the solution was expressed differently in the new process and that it and the new lyophilization parameters had been evaluated at SPL and thought to be better. He did not know the purpose of the changes to the lyophilization process and the reasons for the changes were not written or explained in validation documents.

The annual production review for 2006 stated that the new Process resulted higher yields of API % compared to % (Exh. 52B).

It was noted that the Certificate of Analyses (CoAs) for Heparin Sodium USP showed a two year retest date (e.g. Exh. 80). I, CSO Brown, asked Dr. Y. Wang what might degrade Heparin API and he stated that heat, acid, chemicals, nitrous acid and enzymes could be expected to act as degradants. He stated that the active pharmaceutical ingredient (API) Heparin had been around for 60 years and that the USP potency test, a biological assay (Exh. 64), showed 4-10% assay value variation, was the test performed on aged samples of the API that were and had been in the stability program (Exh. 74). The other tests performed at each station were LOD, pH, Appearance and Total Microbial Count. He stated that the potency test method did not measure any potential degradation products of heparin or impurities in the heparin API. He stated that there had been no examination of impurity that may show up in the API, such as by a forced degradation study. Should the API become degraded, there was no test method at release (Exh. 73) or on stability (e.g. Exh. 74) established to identify the impurity or to measure it's amount.

Stability tables for all Heparin Sodium USP batches that have been involved in the program were provided (Exh. 74) and raw data was spot checked by both Chemist Gu and myself.

Dr. Y. Wang stated that, since the firm performed the Total Aerobic Microbial Count test at each stability station, that an impurity profile for bacterial content was clearly established (see FDA483 #4). He stated that bacterial load also might be indicated by Loss on Drying test results, since the API was hygroscopic.

Dr. Y. Wang stated that testing for Herbicide, Antibiotic and Pesticide (HAP) was performed on CZSPL API by SPL. The results were not provided during the inspection.

The 1/05 process validation failed to identify the attributes of the API that might be changed using the new raw material acceptance criteria and the new process parameters.
Without adequate identification of process impurity and of potential degradation impurity, the improvement offered by the 1/05 approved process and the ability to detect differences as the product ages has been limited.

Dr. Y. Wang stated that the critical steps would be identified and that a process validation would be completed within 6 months. I stated that impurity testing for non-heparin components, some that were already known be included in their evaluation, in process, at release and on stability.

3. The manufacturing instructions for Heparin Sodium USP are incomplete in that they do not include a description of manual manipulations of the during processing steps, they do not include the actual, manually entered lyophilizer set temperatures and times and, operator observations, such as level measurements, used in calculations, during the peroxide step are not recorded.

The lack of a written description for the actual operating practice for the Exh. 49) was discussed in the Product Coverage section of this EIR. Mr. W. Ruan stated that the procedure would be made clear. Notably, there was no time limit for the operations performed and they included steps for which heparin was in solution in and with operations frequently took several hours (e.g. Exh. 37 pg. 10,11 & 22). The risk of heparin degradation during the lengthy operations and the risk posed by the manual interventions necessary for switching and cleaning out the equipment had not been evaluated.

The lack of records for the actual settings entered into the lyophilizer has already been discussed as part of FDA483 #1&2. The lyophilizer was the only shared piece of equipment in the Heparin purification process. The use and cleaning procedure was provided (Exh. 51) and the written procedure did not describe recordkeeping for manual setting of each parameter for the equipment. Dr. Y. Wang stated that the firm would be purchasing software for the lyophilizer in which the settings would be fixed.

It was noted that the reaction times in the batch record were normally expressed with a range of time. There was no criteria given in the manufacturing instruction to the operator for when to use the short time and for when to let the reaction go for the longer time period. For example, for the step, the reaction was heated for hours (e.g. Exh. 37) and then cooled to °C to stop the reaction. The step involved a minute heating step (e.g. Exh. 37), and the step was minutes in length.(e.g. Exh. 37). Temperature and chemical effects on heparin impurity generation during the process has not been evaluated for any of the heparin purification steps and in particular for those steps that use heat. The manufacturing instruction also included a step where the heparin paste was dissolved in unspecified "hot" WFI, near the end of the process, when the lyophilizer feed solution was made (Exh. 37). WFI at the firm was reportedly circulating at between 80 and 90°C.

Review of the reprocessing records showed that API lot #1060-06-0051 was reprocessed from an OOT low potency lot (Exh. 45). The Production Manager stated that for the step (Exh. 45 pg 10), the amount of necessary was calculated and entered into the batch record. The PE tank volume tapes and marks had been used, prior to the recent flowmeter installation, to tell if the total tank volume was reched. When I asked about the origins of the volume used in the calculation (that had a cross out) he stated that the volume of material that was originally in the the ST-1 or ST-2 tank was observed by the operator from a level indicator and the chart (Exh. 50) was used to translate the tank level into a tank volume. It was noted that there were no level indicator readings in the batch records (e.g. Exh. 37).

The currently approved manufacturing instruction for lot #1060-07-0015 (Exh. 37) was also incomplete in other ways including:

After the addition of (e.g. Exh. 37), there was no verification that solution was achieved.

Copies of actual labeling were attached to the Packaging record (Exh. 37 pg. 51-60) and not label specimens. I stated to Mr. W. Ruan that actual label copy should be kept. Approved label templates and label specimen paper was provided (Exh. 38).

Also of note:

steps, including the , showed a minimum settling time (NLT hours) with no maximum. Typical setting actual times were over hours for the . There has been no evaluation of the settling times and whether or not the purity of the resultant material changes.

In most of the manufacturing steps that included changes to the of a solution, the word slowly (e.g. Exh. 37) was used without a cautionary note about the risk to the product or what parameter to watch while the pH changed is accomplished (e.g. temperature). In addition, it was noted that, while the batch record had several spaces for adjustments, they were not observed used. The total volume of or was recorded on a single line on the batch sheets; no result print outs were attached to the batch record. Any interim pH values obtained were lost, along with incremental or volumes added.

Dr. Y. Wang stated during the discussion with management that the lyophilizer automation upgrade would be installed shortly.

4. There has been no test method verification performed for the reported USP test methods, Nitrogen Determination, Protein and Total Aerobic Microbial Count, employed in testing of heparin Sodium USP and Heparin Crude materials, to show that the methods are suitable under actual conditions of use. In addition there is no routine test for ethanol residue amount at the time of release.

There has been no test method verification performed for the reported USP test methods, Protein (Exh. 70A) employed in testing of Heparin Sodium USP (API) and Heparin Crude, and also no test method verification performed for the Nitrogen Determination (Exh. 71A), test and Total Aerobic Microbial Count (Exh. 78A) used for the API. The procedure followed for verification was called assay suitability (Exh. 81). Initial review of the verification data provided prompted inquiry for more information. Mr. Y. Wand stated that they has shared all that they had with us.

Test method verification information was provided (Exh. 70B, 71B & 78B) and was deficient. For the Nitrogen and the Protein tests, the data provided (Exh. 70B, 71B) appeared to be training information: it showed that two analysts had performed the test method according to the written Test Methodology (TM) and that the test sample(s) had passed the tests. The protein test information provided appeared to be testing of in process material and testing of API, all samples from one batch. The analysts did not test the same samples. The information provided no information about the suitability of the test for the items being tested, that is, the accuracy and the limit of detection. There was no indication that the presence of protein in a finished product sample would be detected, nor at what level it would be reliably detected, and, only one batch of API was tested, with no Heparin Crude batches tested. When I asked how much protein needed to be present for the test to detect it, Dr. Y. Wang stated that they had verified the test method, because it was a USP method, but the firm had not done test method validation to find out the limit of detection for the method. The suitability for use of the protein method for in-process testing was also not established, data from only one lot was gathered.

The Nitrogen Determination was an acidic digestion followed by a potentiometric titration. Again, the verification information provided (Exh. 71B), showed that two analysts could test a sample by the TM (Exh. 71A). The information provided no information about the suitability of the test for the items being tested, that is, the accuracy and precision. Two API lots were tested; each analyst tested one lot. Notably, when a lot had failed the test in 2005 (see FDA483#5) the investigation did not indicate that anyone at the firm had any idea what extra nitrogen would mean had contaminated the product. When I asked Dr. Y. Wang if the nitrogen could have meant that there was protein or nucleotides in the product, he stated that the API had no protein in it.

For the microbial test performed on API lots at release and on stability, the method verification did not include the testing of duplicate samples and involved only one lot of Heparin. The identification of the colonies that grew was included in the results for the sample that had to be removed a day early because of high numbers of organisms.

It was noted that low counts were observed on occasion in stability samples analyzed (Exh. 74). The number of organisms found were inside of the specification and were not identified. There was no testing performed that would identify objectionable organisms that may be found in the API.

In addition, there was no routine test for ethanol residue amount at the time of release (Exh. 73), the solvent removed with water, in the final isolation step, a lyophilization (Exh. 37).

There was no discussion of this item during the exit interview.

5. Investigations into failed lots and out of trend lots were approved as complete, but did not identify a root cause for the problem. For example,

Heparin sodium USP batch 1060-05-0001 failed the Nitrogen Determination test and was reprocessed to make 1060-05-0023 without finding the reason for the slightly high, OOS result.

Investigations into OOT of customer absorbance specification for Heparin Sodium USP lots 1060-07-0015 and 1060-06-0049 and the failure of lot 1060-04-0010 were performed without knowing what the failed test measurement actually represented.

Investigations into ROI out of trend results for Heparin Sodium USP lots 1060-05-0010 and 1060-05-0011 identified both results inappropriately, as outliers.

The quality unit was conducting investigations without establishing preventative action such as analyst training or finding the scientific basis for the results of concern.

Four ROI investigations were identified on the Lab Investigation Reports list (Exh. 58) and also appeared in the annual production reviews (e.g. Exh. 52C). Mr. W. Ruan stated that after the APR issuance that they had gone back to look at the OOT ROI results and had declared them outliers. He stated that in 8/07, the procedure was changed and that outliers were not to apply to invalidation of data from chemical test results, only to microbiological-type test results (see SOP-Exh. 55 pg. 13-14). Notably, the written procedure does not identify a specific outlier test to be used. I stated that the risk of identifying results as outliers that were not, was that the investigation into the results would be ended and the root cause remain unidentified, so that preventative action could not take place.

Investigations into OOT of the customer absorbance specification at for Heparin Sodium USP lots 1060-07-0015 and 1060-06-0049 (Exh. 44)(Exh. 52A) and the failure of lot 1060-04-0010 (Exh. 52C) were performed without knowing what the failed test measurement actually represented. Dr. Y. Wang stated that he did not know what the API criteria for a customer at actually meant. It was noted that the firm has conducted investigations into failure and OOT values in API for the Absorbance at and I stated that I did not understand how an investigation could be conducted scientifically when the value of the test and the test result were not clear.

Heparin sodium USP batch 1060-05-0001 failed (Exh.46A) the Nitrogen Determination test and was reprocessed (Exh. 46C) to make 1060-05-0023 without finding the reason for the slightly high, OOS result (Exh. 46B). I asked Dr. Y. Wang about the 2005 lot with the Nitrogen determination failure, he said that it was probably not protein, and pointed out that the lot had been only a little over the specification. The investigation had not considered the ways in which increased amounts of nitrogen might show up in the API, such as protein contamination.

In addition, CR#459753 for lot 1060-06-0051 was reprocessed from 1060-06-0035 an atypical low potency batch (Exh. 45). Reprocessing (from 1060-07-0035-OOT low potency(Exh. 45 pg. 1))was performed 12/06 and the batch released 1/07. The re-processing used slightly more hot WFI (by 10%) during (Exh. 45 pg. 10) with no deviation report. Shipping documents were collected (Exh. 63).

I asked Dr. Y. Wang about a 2005 API lot with a Nitrogen Determination test failure and he said that it was probably not protein, and pointed out that the lot had been only a little over the specification. The investigation had not considered the ways in which increased amounts of nitrogen might show up in the API, such as protein contamination.

During the exit interview inaccuracies in this item were corrected.

6. Heparin Crude lots CSP609054, CSP-609055 and CSP-609056, received from vendor Changzhou Techpool Pharmaceutical Co. Ltd that included material from an unacceptable workshop vendor were used in Heparin Sodium USP 1060-06-0037 & 1060-06-0051 marketed to the USA. In addition, prior to 3/06 there are no blend records from vendor Changzhou Techpool Pharmaceutical Co. Ltd showing the source for their crude materials.

(see Raw Materials Section of this EIR) There was no discussion of this item during the exit interview.

7. The inside surface of large, "cleaned", polyethylene tanks used in the final and step, after both filtrations, were very scratched; with unidentified material adhering to the insides and, the inverted handles held liquid, which spilled to the bottom of the tank when it was uprighted. There was no written procedure showing that the tanks were dedicated to a particular process step. There was no data collected to verify marker and tape volume markings on the outside of the tanks, and, the cleaning method was not validated. It was noted that cleaning tags were made of paper and taped to the outside of equipment unprotected from liquids used in the processing room environments.

Dr. Y. Wang provided a 1060 process flow chart which identified, in a general way, the containers used in the various purification steps (Exh. 8). Mr. Q. Jiangen stated that the tanks that were not identified as made of polyethylene (PE), up to but not including the step (Exh. 9 pg. 1-2) were glass lined vessels, vessels used for the step and forward, that were not designated as PE tanks, were stainless steel tanks. On 2/22/08, I, CSO Brown, accompanied by Mr. Q. Jiangen and Mr. W. Ruan, proceeded to the cleaning Room 303 and turned over one of the largest PE tanks (approximately 100 gallons); it was marked "clean" on a piece of white paper taped onto it's outer surface. Mr. W. Ruan stated that the cleaning method for the tanks had not been validated. It was later provided and is part of a written SOP (Exh. 48). In addition, Mr. W. Ruan stated that there was no data remained to show the calibration for the volume markings on the outside of the PE tanks (some in marker, some on tape with marker markings).

Mr. Q. Jiangen stated that the largest tanks were dedicated to use in the post- adjustment step (Exh. 8 pg. 4), just prior to the freeze dryer loading step. Mr. W. Ruan stated that there was no written procedure describing the "dedication" of these tanks to particular manufacturing steps. With a white cloth provided by the firm, I, CSO Brown, pressed the cloth across the scratched surface on the bottom of the tank; making a noise and showed them the deep scratches covering the inner surfaces (flat bottom and sides). It appeared that material had been routinely scraped off the bottom part of the tank. I also scratched a piece of dark grey material off of the inner side surface, near the bottom of the tank. I stated that the tank was not clean and that the plethora of scratches provided hard to clean surfaces where foreign materials, including objectionable microorganisms, might exist.

One of the middle size PE tanks, also marked "clean", was also uprighted. Mr. Q. Jiangen stated that it was dedicated to use in the step, after the (Exh. 8 pg. 3). When the vessel was turned upright, a clear liquid, which had been inside a hollowed out handle, a part of the molded PE tank, fell to the bottom of the vessel. This vessel also had a plethora of deep scratches on the bottom surface. It appeared that material had been routinely scraped off the bottom part of the tank. I, CSO Brown, stated that the tank was not clean and was not cleaned properly. I stated that the tanks were not appropriately designed for use in this manufacturing environment and were not appropriate for further use.

A written SOP describing the "cleaned" tags was reviewed (Exh. 57). Mr. W. Ruan stated that the tags were not kept. I stated that given the wet manufacturing environment, it was doubtful that many of the tags would survive for long. I, CSO Brown stated that Quality Unit needed a record for each piece of major equipment that showed the status of the equipment at particular times and to show that production was following the cleaning procedures.

On 2/25/08, Mr. Y. Wong stated that the largest size PE vessels would be replaced with a stainless steel tank as soon as possible and that the other tanks would undergo cleaning validation and be employed for another six months. I re-stated that the tanks were no longer appropriate for use.

Dr. Y. Wang stated that the tank would be changed immediately. Discussion of the non-smooth condition of the other tanks and the affect on the quality of the API ensued.

8. Raw material inventories were incomplete in that samples removed from the containers and the status and the amount of materials returned from use by the production processing department were not recorded. For , stored in a freezer, the amount, condition and date of return was not recorded.

(see Product Coverage section of this EIR) There was no discussion of this item during the exit interview.

9. Control of material flow in the processing area was inadequate in that waste protein was carted through a door to the outside in the processing area and not provided for by the material flow written procedure.

A materials flow and people flow diagram was made at the team's request (Exh. 4 pg. 3); during the walkthrough, inquiry about a battered door, leading to the outside, between Rooms 301(crude processing and 303 (cleaning) showed that the door was opened to facilitate the transfer of waste protein out of the heparin processing area, to CT. The door, located at the end of the corridor between the rooms, was not shown as used for material flow on the diagram provided (Exh. 4 pg. 3). Current written procedures about material (Exh. 6A pg. 4) and personnel (Exh. 6B pg. 4)flow in the Heparin manufacturing areas also did not provide for waste handling through the door at the end of the corridor, the actual practice.

There was no discussion of this item during the exit interview.

10. The outer foil bags containing Heparin Sodium USP lot 1060-07-0019, manufactured and held since 5/25/07, are not labeled. The drum lid showed the only indications of the lot number.

(see Product Coverage section of this EIR). There was no discussion of this item during the exit interview.

Dr. Y. Wang stated that this would be fixed before the next batch during the exit interview.

11. There is no report or data to show that leachables for the polyethylene bags used to hold Heparin Sodium USP lot, have been evaluated.

Dr. Y. Wang stated that the polyethylene bags used as the primary API containers were shipped here from SPL. He stated that information about the qualification of the PE bags resided at SPL and that it would be requested. The poly bag information was not provided (Exh. 41 & 27).Review of the specification showed IR testing performed.

I, CSO Brown, stated during the exit discussion, that in light of the kind of events triggering the recalls and the lack of an Ethanol residue test, leachables testing would be appropriate.

ATTACHMENTS

FDA 483 Inspectional Observations (3pp)
Receipt for Samples dated 2/21/08
Receipt for Samples dated 2/25/08

EXHIBITS

1. Organizational Charts and Management Information (5pp)
2. quantity in MMU of 1060 sent to USA by lot
3. Customer List
4. site map, building layout and material flow through 1060 manufacturing areas (3pp).
5. 2004-2007 Sales to USA (4pp)
6. A. Material Flow SOP (8pp) B. People Flow SOP (9pp)
7. Hangzhou Ruihua address
8. 1060 Process Flow Diagram (4pp)
9. Water System Diagram (2pp)
10. Raw material vendor list
11. Heparin Crude Specification
12. Heparin Crude Test Methods (5pp)
13. Warehouse Raw Material Receivals (62pp)
14. Alternate raw material supplier approval SOP (no pg. 11-missing SOP pg. 8)(11pp)
15. New Crude Heparin Supplier Approval (9pp)
16. Approved workshops from which Techpool can obtain Crude Heparin

17. Approved workshops from which Hangzhou Ruihua can obtain Crude Heparin (2pp)
18. Unacceptable Techpool workshop sources as of pre-audit in 2006
19. 2007 Audits Criteria Translation (6pp)
20. Changzhou Techpool (and workshops) Vendor Qualification Report dated 9/10/07 (191pp)
21. Hangzhou Ruihua Biochemical Vendor Qualification Report summary dated 9/10/07 (7pp)
22. Comparison of 1037, 35 and 60 processes for Viral Inactivation Considerations (8pp)
23. A. Virus Study Information (74pp) B. Virus Study Information (69pp) C. Virus Study Information (78pp) D.(106pp) E.Adventitious organism safety evaluation (11pp) F 2007 Risk Management Report (33pp).
24. QU unreviewed PCR list
25. API lots from RM by lots list 2004-2007 (3pp)
26. Change Control historical for Heparin MI (10pp)
27. Plastic PE bag info (3pp)
28. Heparin Crude worksheet not updated for lot CSP-609047 dated 7/24/06
29. RM Inventory Cards for 0706006, C20070631, C20070315 & C20070314 (4pp)
30. Lab Sheets for C20070631, C20070632 (8pp)
31. Hangzhou CoAs for C20070632 &C20070631 (2pp)
32. Hangzhou blend records for C20070314 & C20070315 (4pp)
33. 1060-07-0019 FP test and RM CoAs and test records (5pp)
34. Cleanup record after 1060-07-0028 (3pp)
35. 1060-04-0005 batch record (44pp)
36. 1060-05-0030 (47pp)
37. 1060-07-0015 BR and Packaging/Labeling Record (62pp)
38. Approved labeling materials (3pp)
39. Test sheets for all Heparin Crude missing from Lab Receipt records (24pp)
40. Heparin Crude historical Specification changes (3pp)
41. PE bag historical Specification changes (2pp)
42. A. PV 1/03 report (7pp) B. PVP 11/04 (22pp) C. PV 1/05 (9pp) D. MI changes (2pp)
43. firm traceback (from requested blend records) of the initially recalled lots & (their) selected other 2007 lots to workshops
44. 1060-06-0049 Quality Observation Record for OOT Absorbance at (2pp)
45. Reprocessing protocol for OOT low assay 1060-06-0035 to 1060-06-0051 (CR ref) (10pp)
46. A. Test Record & batch record for OOS 1060-05-0001 (High Nitrogen)(47pp) B.lab investigation and Quality Observation sheet (6pp) C. Reprocess batch record 1060-05-0023 (48pp)
47. Acid and Base preparation sop (7pp)
48. Cleaning SOP for areas and PE tanks (12pp)
49. operation SOP (6pp)
50. Tank volume tables for ST-1 and ST-2 (2pp)
51. Lyophilizationb Operation and cleaning (13pp)
52. A. Annual Product Review 2006-7 (29pp) B. Annual Product Review 2005-6 (33pp) C. Annual Product Review 2004 (29pp).
53. APR SOP (4pp)
54. Deviation SOP (12pp)

55. Lab Investigations SOP (22pp)
56. Quality observation reports (6pp)
57. Heparin area and equipment cleaning SOP (12pp)
58. 2004-2007 OOS List
59. 2004-2007 Deviation List (6pp)
60. 2004-2007 Quality Observation List
61. Sampling SOP (11pp)
62. USDA certificate (2pp)
63. Shipping documents for 1060-06-0051 (7pp)
64. RM & API Potency TM (20pp)
65. None
66. None
67. None
68. None
69. None
70. A Protein TM (7pp)
    B. Protein TMV (6pp)
71. A. Nitrogen Determination TM (6pp)
    B. Nitrogen TMV (6pp)
72. heavy Metals TM (12pp)
73. API Heparin Sodium USP specification
74. all stability (22pp)
75. lyophilizer PQ excerpts (7pp)
76. RM and BR excerpts for Heijiang Heparin Crude use (10pp)
77. pH TM (7pp)
78. A. Micro TM (8pp) B. Micro TMV (8pp)
79. Sampled RM Selected CoAs (2pp)
80. Sampled API CoAs (2pp)
81. Assay Suritability SOP (7pp)

Regina T. Brown (for Dr. Z. Gu)

Zi-Chaing Gu, Chemist

Regina T. Brown

Regina T. Brown, Investigator

Establishment Inspection Report		FEI:	**3005403951**
Changzhou Techpool Pharmaceutical Co. Ltd.		EI Start:	02/27/2008
Changzhou, China		EI End:	02/28/2008

SUMMARY OF FINDINGS

This was a limited inspection of a manufacturer of starting material for heparin sodium active pharmaceutical ingredient and was initiated as the result of the Baxter nationwide recalls, FACTS Assn. Id. 929171, Op. Id. 3628261, a CDER request for coverage of Heparin Sodium; this firm is a manufacturer and tester of Crude Heparin Sodium that is sold to Changzhou SPL to make USP grade active pharmaceutical ingredient (1060). Crude Heparin Sodium from this facility is also exported, as is, through Changzhou SPL to Wisconsin SPL for further manufacture (1035).

This was the initial inspection of this facility.

Management refused to provide copies of records requested during this inspection. A record review was performed. A walk through of the manufacturing facility and warehouse was performed. No samples were collected at the facility. There was no FDA483 issued.

ADMINISTRATIVE DATA/HISTORY OF BUSINESS/INDIVIDUAL RESPONSIBILITY

On 2/27/08 I, Regina T. Brown, Investigator, NWJ-DO, Dr. Zi-Chiang Gu, Chemist, CDER OC and Mr. Bruce Ross, Health Attaché, HHS, Embassy Beijing identified ourselves to Mr. Ding Jianwen, General Manager, who did not speak English. He stated that he was aware of the recalls of heparin in America. We were also greeted by SFDA representatives *Mr. Yuan Liu, Drug Center (Nanjing)), *Mr, Wei Chen, GMP Inspector (Nanjing) and *Ms. Bei Xue, Deputy Director (Changzhou). Mr. Y. Liu and Mr. W. Chen both stayed for the entire inspection day and were also present on the second inspection day. Mr. J. Ding stated that his firm was not regulated by the SFDA and that he had welcomed SFDA to the establishment for this inspection.

Inspected firm:	Changzhou Techpool Pharmaceutical Co. Ltd.
Location:	1 Changhong West Road, Hutang Town Wujin, Changzhou, China
Phone:	86 50986567888
FAX:	86 51986558802
Mailing address:	1 Changhong West Road, Hutang Town Wujin, Changzhou, China
Dates of inspection:	2/27/2008, 2/28/2008
Days in the facility:	2
Participants:	Regina T. Brown, Investigator Zi-Chiang Gu, Chemist

Mr. J. Ding stated that the production workshops were open 24/7 and that the offices were open 8am-5pm six days a week. There were 90 full time and part time employees of the firm. Mr. J. Ding introduced Department Managers to the team (Exh. 1), as follows:

*Mr Deng Jiango, Vice General Manager
*Mr. Zhang Hua, Manager Production
*Ms. Li Li, Manager, Quality Assurance

All department Managers participated in this inspection by responding (with translation) to our (translated) questions during the walk-through of the manufacturing facility as well as during the record review. Dr. Z. Gu performed all the translation duties during this inspection. Mr. B. Ross took photographs, as directed by R. Brown, during this inspection. This report was written by myself, R. Brown.

Mr. J. Ding provided us with an organization chart for the Departments (Exh. 1). He stated that the firm was 45% owned by a Joint Venture (JV) with Changzhou SPL (CZSPL), since 1999. He stated that the relationship was exclusive; that is, Crude Heparin Sodium, the subject of the JV, has been sold only to CZSPL since the beginning of its manufacture in 2002, with none going to any other domestic or international markets. Mr. J. Ding stated that before the JV, Changzhou Techpool (CZTP) had sold Crude Heparin Sodium to Pharmacia. Mr. J. Ding stated that the remainder of the firm was owned 74% by Guandong Techpool and 26% owned by Shanghai I. Industrial Co. The Chairman of the Board for CZTP was David Strong (no address obtained). The office address of Board Member Mr. Fang Yao (Exh. 4) was provided and, he was the person to whom Mr. J. Ding reported. Mr. J. Ding contacted Mr. Y. Fang during this inspection for advice about the progress of the inspection and about providing copies of documents to the team.

The other active pharmaceutical ingredients (APIs) (and intermediates) made by this firm were for the Chinese market (Exh. 2), except as noted below.

Ulinastatin
Urokinase
Low Molecular Weight Heparin Calcium
Iron Sucrose
Low Molecular Weight Heparin Sodium for Japan
Galanthamine Hydrobromide

Mr. J. Ding stated that the Low Molecular Weight Heparin APIs were made in small quantities from Heparin Crude USP (1060) purchased from CZSPL. Mr. J. Ding stated that the firm also manufactured Galanthamine Tablets, from the API (made here) from a plant extract that was purchased.

According to Mr. J. Ding, the factory was built in 1994 by the local government and shares had been purchased by CZTP since 1996 and until 2006, when the site was purchased by CZTP. Mr. J. Ding stated that the factory had 5 workshops, one of which was dedicated to Crude Heparin Sodium manufacture. He stated that the technology used at this facility for the manufacture of Crude Heparin Sodium was transferred to the site from the USA. According to Mr. Ding, CZTP produced just under 70 batches a year and each took about 5 days to complete. Mr. J. Ding stated that the firm was not in production at the present time because of the Spring Festival Holiday, which had just ended. A process flow chart was provided for our review. He pointed out that Crude Heparin Sodium shared some systems with the other products such as the warehouse, stability chambers and the laboratory.

Mr. J. Ding was asked if the firm re-issued Certificates of Analysis (CoAs) for Crude Heparin Sodium sold to CZSPL. After consulting with the Quality Control Manager (who was not identified to the team), Mr. J. Ding stated that the price was usually negotiable when the potency did not match CZSPL's expectations. He stated that the CoAs were never changed to a different value than that obtained by the laboratory and that lots were not retested. Mr. J. Ding stated that only once, this establishment had mixed a lot a second time and then assayed again. There was no response to a question posed about the presence of a written record of the remixing procedure followed.

Mr. J. Ding stated that before 3/06, when the first vendor workshop audits occurred, this establishment had identified source workshops for crude heparin by itself. He stated that the currently approved CZSPL workshops (Exh. 3) were the only ones used and that each portion or bag of crude heparin material received was tested for potency and by UV (260/280). He stated that he relied upon the workshops to provide exclusively porcine origin heparin and that CZTP did not perform any testing for species origin of the heparin.

On 2/27/08, Mr. J. Ding stated that we would not be provided with copies of the documents that we had requested during our record review. The refusal to provide copies of requested documents was repeated on 2/28/08 (see Refusal section of this report for a list of the documents that we had requested).

The inspection was concluded on 2/28/08. The exit interview was done in the presence of all persons with the names asterisked and Mr. J. Ding. In addition to the observing SFDA persons Mr. Y. Liu and Mr. W. Chen, Mr. Yang Quo Liang, Director, SFDA, Jiangsu Province (Nanjing) and Mr. Ye Yao Yu, Deputy Director, Sr. Engineer SFDA, Jiangsu Province (Nanjing) attended the exit discussion. During the exit interview I, R. Brown stated that the team had identified a degree of accountability as far as tracing back to the workshops and slaughter houses was concerned, but that we would be unable to demonstrate that in our report. I also stated that a change to closer to cGMP for the Heparin workshop activities would be welcomed.

PRODUCT COVERAGE

During the walk through of the warehouse and the dedicated Heparin purification facility, Mr. Ding stated that the raw material arrived in chunks and also in granular form; there was none stored at the facility during this inspection. Inventory records were manual and original data about the amount of raw materials actually available for use was recorded only on a card, called a "hoycard". The hoycard was physically associated, but not attached to containers of the materials stored. Containers in a lot were numbered and their consumption was noted and dated on the hoycard.

During the walk through, photos of one of five unopened brown bags of medicinal grade, government certified, polyethylene bags were taken along with photos of an opened 1060 bag, with handwritten amounts and a hoycard were obtained (Exh. 6, 7 & 8). All warehoused materials observed during the walk through had a hoycard; however, during the walk through it was noted that material could be stored temporarily in the warehouse and not receive a hoycard (see below).

Crude Heparin Sodium was stored in a large locked room. The warehouse was not temperature controlled; reportedly, in the summer humidity got as high as 30% and the temperature inside varied between 12°C -50°C with the seasons.

During the manufacturing area tour, it was noted that the last batch made and released was 709066, the 66th and final batch of 2007.

Mr. J. Ding stated that there were two processes for purifying the heparin; he stated that for some of the crude heparin there were no pH adjustments made and they started at a later stage on the same batch record master (these would start at step 4, in the list below). Record review showed both processes used; the criteria for eliminating the pH adjustment steps was not made clear. The full process was described as follows:

1. Dissolve crude heparin sodium in a stainless steel tank containing a 3% NaCl solution (approximately 7-8w/w)
2. Adjust pH to 5 & stir 2 hours
3. Adjust pH to 7 & divide solution into 4 large Polyethylene (PE) Tanks
4. Add 95% ethanol/water to a density measurement of 50-60% alcohol
5. Let precipitate fall out for about 20 hours. Decant.
6. Add 100% ethanol and hand stir with a plastic paddle to dehydrate the heparin. Decant & transfer solid mass to cloth bags to further (drip) dry.
7. Place each PE Tank load into the Fluid Bed Drier (FBD) for 3-4 hours. Weigh.
8. Air Oven Tray Drier at 95°C for 7-8 hours
9. Mill
10. Blend in Drum Blender for 1 hour (see Exh. 5)
11. Sample each container and test potency
12. Package into 25 kg PE bags (Exh. 6)

It was noted that the PE Tanks were scratched on the bottom. Mr. Z. Hua stated (translated) that if the material dried in the PE Tank (while waiting to be FBD dried), it got very hard and had to be scraped out of the PE Tank.

It was also noted that the 2-sock FBD was about 5 feet high with a bowl diameter of about 4 feet. The bowl gasket was attached and not removed for cleaning.

The Heraeus Air Oven Tray Drier had a gauge that went as high as 300°C and the operator said that the government calibrated it. Mr. Z. Hua stated that a knob, turned to the number 9 on the top front of the oven, was the temperature control and that the knob was never moved off of the 9. The oven temperature at 9 was reportedly 94°C. He stated that the temperature was read once in the drying time and that reading was recorded on the batch record.

A partial brown bag of medicinal grade PE bags was noted in the milling, blending and packaging room.

Mr. Z. Hua stated that after the Air Oven Tray Drier step, the material was sometimes placed into PE bags and stored in the warehouse. He stated that there were no QA labels for the stored in-process material other than a handwritten one, which the operator made out, with the batch number, the weight and the date. He stated that the stored material would not get a hoycard.

Mr. Z. Hua stated that before 10/07 the potency records kept in the area used for the blending operation, were in notebooks and that now, potency sample results were on the batch records. Record review showed all 2006 and 2007 test results on the Crude Heparin Sodium CoAs were from results from test data and results recorded on the batch records.

We obtained for review the raw material heparin specifications and test methods as well as the finished product heparin specifications and test methods. The written test procedures did not describe test sample preparation. The tests done on each raw material bag received were potency and a UV measurements at 260nm and 280nm. Review showed that a single receipt could consist of many small bags of crude heparin and we observed in the records reviewed as many as 27 bags in a single receival. 150 receipt and testing records of 2007 raw material sources and test results were reviewed--and those raw materials were either partially or totally consumed in the making of approximately five 2007 CSP Crude Heparin Sodium batches. It was noted that the 260/280 ratio (not calculated by CZTP) varied from 0.6 to 1.8 during the record review. A "normal" 260/280 ratio was not ascertained during this inspection. It was also noted that some crude heparin was not received at CZTP until approximately 6 months after the animal was slaughtered. Mr. J. Ding stated that 3-4 months would be a more routine time interval between slaughter and receipt. These raw material records showed slaughter house, numbers of intestines processed, dates, workshop and the weight of each bag they were, reportedly, records collected and forwarded with the goods by heparin traders.

We were also provided with the manufacturing records (called blend records), Certificates of Analyses (CoAs) and test records for all Crude Heparin Sodium batches made in 2006 and 2007. These records were counted and selected records reviewed and compared to the records of received crude heparin raw materials were investigated to varying degrees: CSP-709028, CSP-709029, CSP-709030, CSP-709049, CSP709046 and CSP709042. Notably, CSP-709004 was the only missing record identified. The warehouse receipt log entries for all raw materials for the CSP batches identified were reviewed.

Review of the CSP-709028 blend record showed the use of all of a raw material lot, -034, and that 27 bags were consumed. The receiving records showed 25 bags of crude heparin received and tested.

It was noted that there was no batch size fixed by the master blend record.

There was no indication in the blend record that a sample had been removed from the batch.

There was no tour of the laboratory conducted.

Mr. Ding stated that they did occasionally have returned product.

COMPLAINTS

Mr. J. Ding stated that there had been one complaint historically and that it had been for another product, not heparin sodium.

REFUSAL

Mr. J. Ding stated repeatedly during the inspection that the Crude Heparin Sodium made at CZTP did not fall under cGMP. Mr. J. Ding stated that Board Member Mr. F. Yao had forbidden him to provide us with copies of the records requested. He stated that the reason for the refusal was that in China, before copies of documents were provided to the government, a public notice was printed, because the collection of records meant that a criminal investigation had begun.

The refusal, on 2/27/08 and 2/28/08, to provide copies of the following documents occurred:

Raw material crude specification
Raw material crude written test method
Crude Heparin Sodium specification
Crude Heparin Sodium written test method
(observed) Hoycard for medicinal PE bags observed in warehouse
CSP-709028 CoA and blend record
CSP-609032 blend record excerpts
CSP-609033 blend record excerpts
2 pages from inventory receipt information for -028 receipt

ATTACHMENTS

DMF except regarding polyethylene bags (2pp)

Establishment Inspection Report		FEI:	**3005403951**
Changzhou Techpool Pharmaceutical Co. Ltd.		EI Start:	02/27/2008
Changzhou,	China	EI End:	02/28/2008

EXHIBITS

1. CZTP organizational chart
2. Product List
3. Approved Workshop List
4. Board Member Mr. Fang Yao office address
5. Copies of drum blender photo
6. Medicinal Grade Polyethylene bag photos (5pp)
7. partially used 1060 and hoycard photos (5pp)
8. Original photodisc (all EI photos are dated 2/26)

Regina T. Brown, Investigator Z. Gu, Chemist

Establishment Inspection Report		FEI:	**3005988989**
Hangzhou Ruihua Biochemical Products Co. Ltd.		EI Start:	02/28/2008
Hangzhou,	China	EI End:	02/29/2008

SUMMARY OF FINDINGS

This was a limited inspection of a manufacturer of starting material for heparin sodium active pharmaceutical ingredient and was initiated as the result of the Baxter recalls, FACTS Assn. Id. 929176, Op. Id. 3628288, and a CDER request for coverage of Heparin Sodium. This firm is a manufacturer and tester of crude Heparin Sodium that has been sold to Changzhou SPL for further manufacture into USP grade API.

This was the initial inspection of this facility.

The firm refused to provide records for review to the inspection team. However, a walk-through of the manufacturing facility, as well as interviews with the General Manager and his Production Manager were begun. No samples were collected. There was no FDA483 issued.

ADMINISTRATIVE DATA

Inspected firm:	Hangzhou Ruihua Biochemical Products Co. Ltd.
Location:	Chenjia #28, Wanshi Township, Fuyang Hangzhou, China
Phone:	86 57183261198
FAX:	86 57183261348
Mailing address:	Chenjia #28, Wanshi Township, Fuyang Hangzhou, China
Dates of inspection:	2/28/2008, 2/29/2008
Days in the facility:	2
Participants:	Regina T. Brown, Investigator Zi Chiang Gu, Chemist

THIS REPORT IS LIMITED TO A COVERSHEET SUMMARY

In the afternoon of 2/28/08, I, Regina T. Brown, Investigator, NWJ-DO, Dr. Zi-Chiang Gu, Chemist, OC, CDER and Mr. Bruce Ross, Health Attaché, HHS, Embassy Beijing identified ourselves to Mr. Ruihua Hua, General Manager, who spoke no English. He stated that he was aware of the Baxter heparin problem in the US and that local police had been speaking to him, since the morning, about our immanent arrival and to expect an inspection. Mr. H. Ruihua stated that his business was not regulated by a Chinese government Agency. Mr. H. Ruihua stated that this was a local firm and that he was the sole owner. Mr. H. Ruihua was distracted by telephone calls from, reportedly, local and provincial government, during both inspection days. Mr. H. Ruihua had a friend named Mr. Jess Hu, who introduced himself to us on 2/28/08. He spoke English and translated the concerns that Mr. H. Ruihua had about the inspection, to the team, on both inspectional days.

Mr. H. Ruihua stated that when the firm was manufacturing Heparin Crude, they were working 24 hours a day seven days a week until it was done, with 4-5 people working in production each 12 hour shift and 7-8 people working in the laboratory. On 2/28/08, Mr. H. Ruihua agreed to let the team walk through the facility. He stated that there was no raw material in-house during our walk through, because the Spring Festival had interrupted everyone's work for the last two weeks.

Mr. H. Ruihua stated his firm used to be larger; that until approximately 2000, he had workers processing porcine intestines and also through the crude heparin purification stages that are still performed at this site. Mr. H. Ruihua stated that an empty warehouse on the property had once been used to hold up to 1 ton of heparin-we did not tour that particular, large building. Mr. Ruihua stated that the blue ear pig disease of last year had only affected the volume of Crude Heparin available and that it did not affect his business in any other way. He stated that the number of pigs slaughtered per year in China had decreased significantly, from 0.6 billion in 2005 to 0.4 billion in 2007. He stated that the crude heparin was very valuable and that workshops handling the pig intestines also sold the intestines as casings to the processed meat industry Mr. H. Ruihua stated that the market for heparin was very competitive and he had seen a recent news story about a person who had been killed for the heparin that he was carrying on his person.

Mr. H. Ruihua stated that Changzhou SPL sent this establishment their production needs and a schedule at the beginning of each year. He stated that his firm has consistently been unable to meet the need because there is not enough heparin available. He stated that the only product made on site was Crude Heparin and that Changzhou SPL was now his only customer. I, CSO Brown, saw a photograph of Dr. Y. Wang, whom we had met at Chanzhou SPL Co. Ltd. in the firm entryway.

Mr. H. Riuhua stated that Changzhou SPL had visited his firm last year and had visited the 10 or 11 workshops that his firm was using a list of workshops that had been sent to this establishment after the visit. He stated that Changzhou SPL had provided him with a list of approved workshops. Mr. H. Ruihua stated that he was no longer able to get crude heparin from a couple of the 10 or 11 approved workshops because they had gone out of business. He stated that the raw material received was crude heparin and is all sourced from workshops outside of the Province Ziejiang. Mr. H. Ruiha stated that, for nearby provinces, his firm sent out a van that went to the workshops and picked up the crude heparin, returning to this establishment with it. He stated that, for workshop locations that were further than a three or four hour drive, his firm had paid representatives, who were located closer to the workshops. He stated that the representatives would procure the crude heparin from the approved workshops and airmail it to this site.

Mr. H. Ruihua stated that the raw material he received was solid and that it did not noticeably degrade if the plastic bag that it came in was left open. He stated that it could vary in color form a light tan granular material to a dark colored block or hard chunks of solid material. Mr. H. Ruiha stated that if the chunks of crude are too dark, it meant that too much alcohol had destroyed the heparin. He stated that the resin had already been removed as part of the workshop process. He stated that each batch of raw material was tested for appearance and potency and that potency was normally <65%. He stated that the firm had complete records; he stated that they had records showing the workshop from which each raw material receival originated and he said he had test results for the tests done here on the raw material. He stated that he also maintained batch records for his product, Crude Heparin and the associated test records. None of these records were observed during this inspection because the firm, under the advice of the local police, refused to show them to us.

Mr. H. Ruihua stated that when his firm has manufactured a batch of either a 50 or a 100 kg size, it was tested in the laboratory on site. Mr. H. Ruihua stated that his company's product, crude heparin, was tested for appearance and potency and that the potency result was usually between 80 and 90 Units/mg). He stated that the firm's van took the finished product, crude heparin, to Changzhou SPL which was about 3 hours away.

We toured a compact manufacturing area, all on the ground floor of a building located just inside the gate, with Mr. H. Ruihua, Mr. J. Hu and a young woman who was identified as the Production Manager. The Production Manager assisted us during the walk-through and stated (through Mr. J. Hu and through Dr. Z. Gu acting as translators) that the raw material was dissolved in water in several large (approximately 500 liter) polyethylene tanks and then pumped into one of four covered, jacketed stainless steel mixing tanks (approximately 250 liter) that had already received a defined volume of ethanol (85% ethanol/water). She stated that the alcohol was siphoned off into blue drums. We noted about 35 blue drums of, reportedly, used alcohol in a back room. She stated that the precipitate was removed, wet, from the stainless steel vessels. The Production Manager stated that the wet mass was hung in bulk amounts in cloth bags. Wet, crude heparin was transported in plastic pails and poured into one of 7 large (approximately 1.5 liter) Buchner filters (with polyethylene filters), set up on the floor in large, repaired Erhlenmeyer flasks.

Mr. H. Ruihua stated that only fresh alcohol was used in the purification process. He stated that the ethanol was re-distilled on site. I, CSO Brown, observed a distillation tower.

The Production Manager stated that the sucked down cake was dried in enamel pans inside of one of eight bench top, steam fueled, air dryers, for about 8-9 hours. She stated that the crude heparin at this step in the process was very hard and was light yellow to off white in color.

Mr. H. Ruihua stated that the dried crude heparin could be bagged and stored at this step, but that, usually, it was milled on the same day as it was removed from the dryers. The mill was in a room by itself that smelled musty. The milled material was blended in the firm's V blender when enough product for a 100 kg (or 50 kg) batch had been processed. We saw a 25 kg bag of lot 20082004 on the shelf. It was light tan colored granules, contained in double polyethylene bags, with a blue handwritten paper label on the outer bag. The tour was completed and it was made clear that the team would return in the morning.

On 2/29/08, Mr. H. Ruihua stated that the local police had spoken to him after we had left and that he was instructed not to allow the inspection to go any further. He stated that we would not be permitted to see any documents and that we would also not be able to walk through the laboratory. He would not share the approved workshop list with us, nor would he state the Province(s) in which the approved workshops were located. The inspection was concluded.

REFUSALS

The owner of the firm refused to provide any records for our review and refused to permit the team to walk through the testing laboratory, on the advice of the local city police.

Regina T. Brown, Investigator Zi Chiang Gu, Chemist

FDA Public Health Update

Recall of Heparin Sodium Injection and Heparin Lock Flush Solution (Baxter)

The Food and Drug Administration is issuing this update to inform the public that

- Baxter Healthcare Corporation has extended its recall of multi-dose vials of heparin sodium for injection to also include single-dose vials of heparin sodium for injection.
- As a precautionary measure Baxter is also recalling its heparin lock flush products. The heparin source manufacturer for lock flush solutions is the same as that for Baxter's heparin sodium for injection.
- Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the US market.

Since FDA learned of the adverse events associated with the Baxter multi-dose heparin vials, the Drug Shortages Team at FDA has been working closely with APP, the other supplier in the US for heparin multi-dose and single-dose vials, to determine their manufacturing capacity. With the verification that APP can now adequately supply the US market Baxter is voluntarily recalling all of its multi-dose and single-dose vials. FDA has also confirmed that there are multiple U.S. suppliers of heparin lock flush products with substantial inventory, making a shortage of these products unlikely.

The recall notice issued by Baxter provides instructions to healthcare providers and institutions regarding the identification and disposition of their product they may have in their inventories. The only Baxter heparin-containing products that will remain on the market are large volume parenteral solutions containing 200 Units of heparin per 100 cc in 500 and 1000 cc total volume bags. No adverse events have been reported in relation to the large volume solution. The heparin source manufacturer for the large volume solution is different from that of the products being recalled.

On February 11, 2008, the FDA issued a public health advisory informing the public about reports of serious adverse events in patients who received bolus injections of heparin sodium primarily from multi-dose vials manufactured by Baxter Healthcare Corporation. A description of the clinical settings and characteristics of the cases of serious adverse events that resulted in the public health advisory can be found at http://www.fda.gov/cder/drug/advisory/heparin.htm.

The underlying cause of adverse events reported for Baxter's heparin sodium is still unknown and remains under investigation. FDA investigators and scientists are working independently and in collaboration with the Centers for Disease Control and Prevention, and Baxter to discover the underlying cause of the adverse events.

FDA continues to monitor its post-marketing safety database for additional cases in the US and abroad related to heparin usage. Health care providers are encouraged to report all allergic-type reactions to any heparin infusion to FDA's MedWatch on line at http://www.fda.gov/medwatch/report/hcp.htm, by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

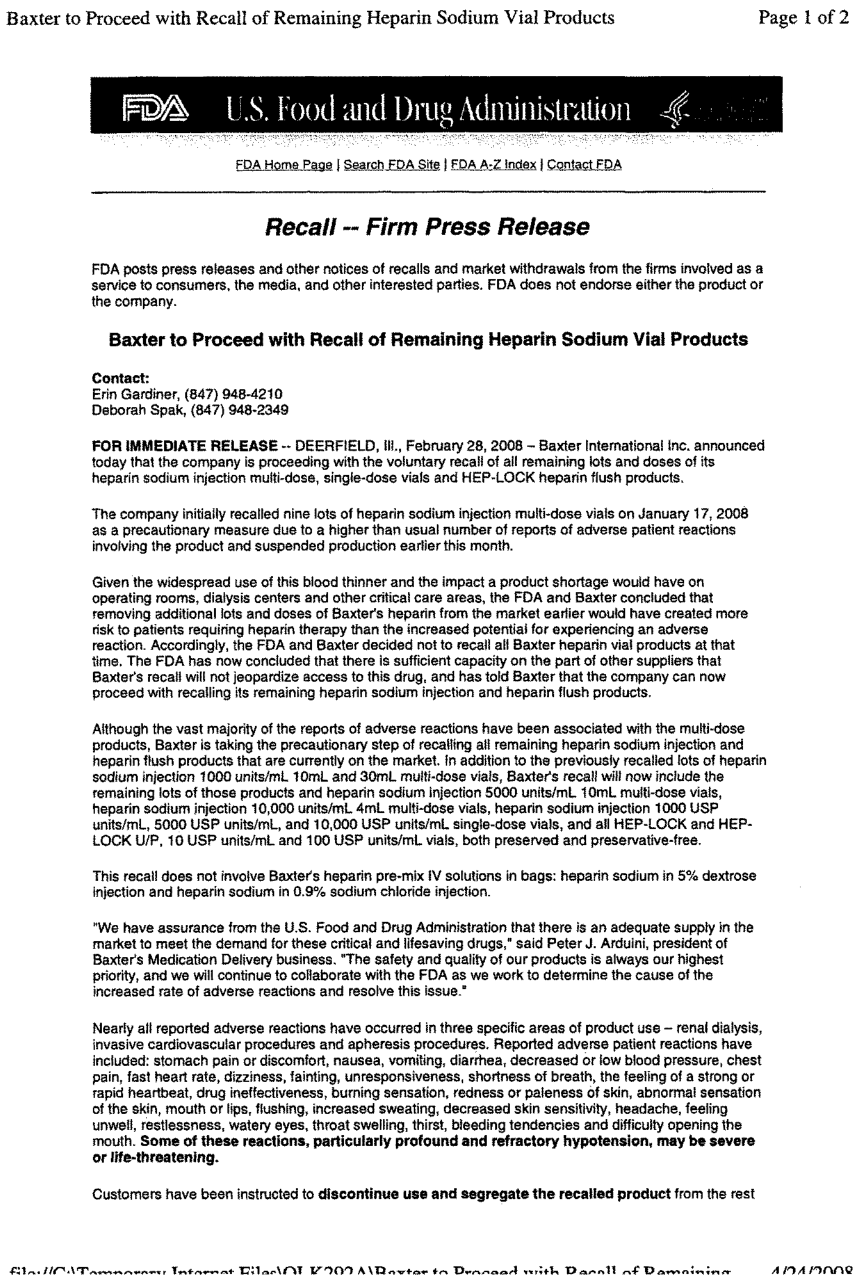
↑ Back to Top ↖ Back to Heparin Information

PDF requires the free Adobe Acrobat Reader

Date created: February 28, 2008

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research



Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

Baxter to Proceed with Recall of Remaining Heparin Sodium Vial Products

Contact:
Erin Gardiner, (847) 948-4210
Deborah Spak, (847) 948-2349

FOR IMMEDIATE RELEASE -- DEERFIELD, Ill., February 28, 2008 – Baxter International Inc. announced today that the company is proceeding with the voluntary recall of all remaining lots and doses of its heparin sodium injection multi-dose, single-dose vials and HEP-LOCK heparin flush products.

The company initially recalled nine lots of heparin sodium injection multi-dose vials on January 17, 2008 as a precautionary measure due to a higher than usual number of reports of adverse patient reactions involving the product and suspended production earlier this month.

Given the widespread use of this blood thinner and the impact a product shortage would have on operating rooms, dialysis centers and other critical care areas, the FDA and Baxter concluded that removing additional lots and doses of Baxter's heparin from the market earlier would have created more risk to patients requiring heparin therapy than the increased potential for experiencing an adverse reaction. Accordingly, the FDA and Baxter decided not to recall all Baxter heparin vial products at that time. The FDA has now concluded that there is sufficient capacity on the part of other suppliers that Baxter's recall will not jeopardize access to this drug, and has told Baxter that the company can now proceed with recalling its remaining heparin sodium injection and heparin flush products.

Although the vast majority of the reports of adverse reactions have been associated with the multi-dose products, Baxter is taking the precautionary step of recalling all remaining heparin sodium injection and heparin flush products that are currently on the market. In addition to the previously recalled lots of heparin sodium injection 1000 units/mL 10mL and 30mL multi-dose vials, Baxter's recall will now include the remaining lots of those products and heparin sodium injection 5000 units/mL 10mL multi-dose vials, heparin sodium injection 10,000 units/mL 4mL multi-dose vials, heparin sodium injection 1000 USP units/mL, 5000 USP units/mL, and 10,000 USP units/mL single-dose vials, and all HEP-LOCK and HEP-LOCK U/P, 10 USP units/mL and 100 USP units/mL vials, both preserved and preservative-free.

This recall does not involve Baxter's heparin pre-mix IV solutions in bags: heparin sodium in 5% dextrose injection and heparin sodium in 0.9% sodium chloride injection.

"We have assurance from the U.S. Food and Drug Administration that there is an adequate supply in the market to meet the demand for these critical and lifesaving drugs," said Peter J. Arduini, president of Baxter's Medication Delivery business. "The safety and quality of our products is always our highest priority, and we will continue to collaborate with the FDA as we work to determine the cause of the increased rate of adverse reactions and resolve this issue."

Nearly all reported adverse reactions have occurred in three specific areas of product use – renal dialysis, invasive cardiovascular procedures and apheresis procedures. Reported adverse patient reactions have included: stomach pain or discomfort, nausea, vomiting, diarrhea, decreased or low blood pressure, chest pain, fast heart rate, dizziness, fainting, unresponsiveness, shortness of breath, the feeling of a strong or rapid heartbeat, drug ineffectiveness, burning sensation, redness or paleness of skin, abnormal sensation of the skin, mouth or lips, flushing, increased sweating, decreased skin sensitivity, headache, feeling unwell, restlessness, watery eyes, throat swelling, thirst, bleeding tendencies and difficulty opening the mouth. **Some of these reactions, particularly profound and refractory hypotension, may be severe or life-threatening.**

Customers have been instructed to **discontinue use and segregate the recalled product** from the rest of their inventory. Customers should then contact Baxter to arrange for return and replacement product. Customers with recalled product purchased indirectly should contact their wholesaler or distributor for return and replacement product. Customers with questions may contact the Center for One Baxter at 1-800-4-BAXTER (1-800-422-9837). Representatives will be available twenty-four hours a day, seven days a week.

#

RSS Feed for FDA Recalls Information [what's this?]

Sign up for Recall email updates.

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff

U.S. Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

Information on Heparin Sodium Injection

Screening Methods (3/6/2008)

Please send all test results to the U.S. FDA.

- Impurity Evaluation of Heparin Sodium by Capillary Electrophoresis
- Impurity Evaluation of Heparin Sodium by ^{1}H-NMR Spectroscopy (updated 3/11/2008)

In early February, after learning about a spike in adverse events involving this product, FDA launched a far ranging investigation in both the United States and abroad. This included inspecting Baxter's domestic facilities, examining Heparin product in the United States and sending a team of experts to China to conduct a comprehensive inspection of the Changzhou SPL facility that makes the active ingredient for this drug.

While the FDA has yet to determine the root cause of these adverse events, we have found a Heparin-like compound that is not Heparin present in some of the Heparin Active Pharmaceutical Ingredient (API) produced by Scientific Protein Labs, which maintains a facility in Wisconsin in addition to the Changzhou plant.

This contaminant is present in significant quantities, accounting for 5 to 20 percent of the total mass of each sample tested. It reacts like Heparin in many tests, which is why the traditional release tests did not detect it.

At this point, we don't know how the Heparin-like compound got into the Heparin Active Pharmaceutical Ingredient, but we are continuing to aggressively investigate the situation.

We don't yet have proof that this contaminant is causing the adverse events. There is an association, but not a direct causal link at this time.

To ensure that all is being done to provide a safe supply of this life-saving drug, we are releasing information on two tests that manufacturers and regulators can use to screen for this contaminant.

The two methods include proton nuclear magnetic resonance (H-1 NMR) and capillary electrophoresis (CE). The tests are to be used for ALL Heparin Sodium API prior to batch release. The API material is considered contaminated if there is a doublet peak at 2.1 ppm in H-1 NMR and a shoulder peak in CE, as illustrated in the two attachments. Heparin sodium API must contain only a single peak (singlet) at 2.1 ppm in NMR and a single peak in CE. It is recommended that both screening methods (H-1 NMR and CE) be used in addition to the regulatory and/or compendial specification requirements.

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

American Health Packaging Announces a Recall of Approximately 1,400 Units of Heparin Sodium Vial Products as Part of Broader Baxter Recall

Units for Pharmacy Automated Equipment Part of Broader Recall

Contact:
Michael N. Kilpatric
610-727-7118

FOR IMMEDIATE RELEASE -- Valley Forge, PA -- March 20, 2008 --- American Health Packaging (AHP), a subsidiary of AmerisourceBergen Corporation (NYSE:ABC), today announced a voluntary recall of 1,421 units (25 vials per unit) of 10000 USP units/ml heparin sodium injection 1ml vials as part of the broader February 29, 2008 recall of Heparin products made by Baxter Healthcare Corporation. The vials were manufactured by Baxter and then placed by AHP into individually labeled bags for use in pharmacy automation equipment. The AHP packages where sold to five hospitals in Georgia and California, all of whom were notified of the recall earlier this month. Baxter Healthcare will reimburse AHP for the recalled product.

The recalled products are APS HEPARIN 10MU/ML (10000 USP units/ml) 1ml SDV 25UD (bag) **NDC # 00641-0410-25**, lot numbers 074155, 073089, 073391, 073613, 070095A, 073712, 072907, 073454, 070095D and APS HEPARIN SDV 10MU (10000 USP units/ml) 1ml 25UD (box and rod) **NDC # 00641-0410-25**, lot numbers 070095B, 070095C, 068286, 067755. AHP instructed customers to return any and all of these product lots remaining in inventory.

This recall was initiated due to the Baxter Healthcare's recall which stated, "**...voluntary recall of Heparin Sodium Injection to include all lots of single and multi-dose vial products**, due to an increase in reports of adverse patient reactions including abdominal pain, burning sensation, chest pain, diarrhea, dizziness, drug ineffectiveness, dyspepsia, dyspnia, erythema, flushing, headache, hyperhidrosis, hypoesthesia, hypotension, **including profound and refractory hypotension**, increased lacrimation, loss of consciousness, malaise, nausea, pallor, palpitations, paresthesia, paresthesia (oral), pharyngeal adema, restlessness, vomiting/retching, stomach discomfort, tachycardia, thirst, trismus, and unresponsiveness to stimuli. The reports of profound and refractory hypotension usually occur with the first few minutes of bolus administration."

This recall is being made with the knowledge of the Food and Drug Administration. Heath care professionals with questions about the AHP packages should contact Richard J. Augustine at 1-800-707-4621. To report adverse drug events or for information on the Baxter Healthcare recall of all Heparin Sodium Injection products, please contact Baxter Healthcare at 1-800-667-0959.

About AmerisourceBergen

AmerisourceBergen is one of the world's largest pharmaceutical services companies serving the United States, Canada and selected global markets. Servicing both pharmaceutical manufacturers and healthcare providers in the pharmaceutical supply channel, the Company provides drug distribution and related services designed to reduce costs and improve patient outcomes. AmerisourceBergen's service solutions range from pharmacy automation and pharmaceutical packaging to reimbursement and pharmaceutical consulting services. With more than $66 billion in annual revenue, AmerisourceBergen is headquartered in Valley Forge, PA, and employs more than 11,500 people. AmerisourceBergen is ranked #29 on the Fortune 500 list. For more information, go to www.amerisourcebergen.com.

FORWARD-LOOKING STATEMENTS

This news release may contain certain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. These statements are based on management's current expectations and are subject to uncertainty and changes in circumstances. Actual results may vary materially from the expectations contained in the forward-looking statements. The following factors, among others, could cause actual results to differ materially from those described in any forward-looking statements: competitive pressures; the loss of one or more key customer or supplier relationships; customer defaults or insolvencies; changes in customer mix; supplier defaults or insolvencies; changes in pharmaceutical manufacturers' pricing and distribution policies or practices; adverse resolution of any contract or other disputes with customers (including departments and agencies of the U.S. Government) or suppliers; regulatory changes (including increased government regulation of the pharmaceutical supply channel); government enforcement initiatives (including (i) the imposition of increased obligations upon pharmaceutical distributors to detect and prevent suspicious orders of controlled substances (ii) the commencement of further administrative actions by the U. S. Drug Enforcement Administration seeking to suspend or revoke the license of any of the Company's distribution facilities to distribute controlled substances, (iii) the commencement of any enforcement actions by any U.S. Attorney alleging violation of laws and regulations regarding diversion of controlled substances and suspicious order monitoring), or (iv) the commencement of any administrative actions by the board of pharmacy of any state seeking to suspend, revoke or otherwise restrict the ability of any of the Company's distribution facilities or businesses to distribute or dispense pharmaceuticals in such state; changes in U.S. government policies (including reimbursement changes arising from federal legislation, including the Medicare Modernization Act and the Deficit Reduction Act of 2005); changes in regulatory or clinical medical guidelines and/or reimbursement practices for the pharmaceuticals we distribute, including erythropoiesis-stimulating agents (ESAs) used to treat anemia patients; price inflation in branded pharmaceuticals and price deflation in generics; fluctuations in market interest rates; operational or control issues arising from the Company's outsourcing of information technology activities; success of integration, restructuring or systems initiatives; fluctuations in the U.S. dollar - Canadian dollar exchange rate and other foreign exchange rates; economic, business, competitive and/or regulatory developments in Canada, the United Kingdom and elsewhere outside of the United States; acquisition of businesses that do not perform as we expect or that are difficult for us to integrate or control; any disruption to or other adverse effects upon the PMSI workers' compensation business caused by the Company's announcement that it is pursuing the sale of PMSI; the inability of the Company to successfully complete the sale of PMSI; the inability of the Company to successfully complete any other transaction that the Company may wish to pursue from time to time; changes in tax legislation or adverse resolution of challenges to our tax positions; and other economic, business, competitive, legal, tax, regulatory and/or operational factors affecting the business of the Company generally. Certain additional factors that management believes could cause actual outcomes and results to differ materially from those described in forward-looking statements are set forth (i) in Item 1A (Risk Factors) in the Company's Annual Report on Form 10-K for the fiscal year ended September 30, 2007 and elsewhere in that report and (ii) in other reports filed by the Company pursuant to the Securities Exchange Act of 1934.

#

RSS Feed for FDA Recalls Information [what's this?]

Sign up for Recall email updates.

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff

U.S. Food and Drug Administration

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

B. Braun's Supplier Recall of Heparin API Prompts Voluntary Recall of Heparin Solutions

Scientific Protein Laboratories LLC (SPL) manufactures Heparin Sodium USP active pharmaceutical ingredient that is used by B. Braun Medical Inc. to produce Heparin Sodium in 5% Dextrose and 0.9% Sodium Chloride Injection solution

Contact:
Stephanie Euler, 908-276-4344 ext. 213
Susan Denby, 610-997-4856

FOR IMMEDIATE RELEASE –Irvine, CA – March 21, 2008 — B. Braun Medical Inc. was recently notified by its supplier, Scientific Protein Laboratories LLC (SPL) of a nationwide recall of Heparin Sodium USP active pharmaceutical ingredient (API). The voluntary recall affects the following 23 Finished Product (FP) lots manufactured and distributed by B. Braun Medical Inc. nationwide and to Canada.

B. Braun FP Lot #	B. Braun FP Material	Description	NDC Numbers	CAN DIN
J7D490	P5872	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	0264-9587-20	N/A
J7C684	P5771	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	0264-9577-10	N/A
J7D496	P5771	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	0264-9577-10	N/A
J7C470	P5872	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	0264-9587-20	N/A
J7D580	P5671-00	Heparin Sodium 20,000 Units in 5% Dextrose Injection (500mL)	N/A	02209713
J7E420	P5872-00	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	N/A	02209721
J7C611	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7C557	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7C477	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7C705	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7D485	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7E415	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7E416	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7E494	P5872	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	0264-9587-20	N/A
J7E500	P5771	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	0264-9577-10	N/A

J7E577	P5771-00	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	N/A	01935941
J7E489	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7N556	P5872	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	0264-9587-20	N/A
J7P404	P5771	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	0264-9577-10	N/A
J7N604	P5771	Heparin Sodium 25,000 Units in 5% Dextrose Injection (500mL)	0264-9577-10	N/A
J7P476	P5872	Heparin Sodium 25,000 Units in 5% Dextrose Injection (250mL)	0264-9587-20	N/A
J7N519	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933
J7N676	P8721	Heparin Sodium 1000 Units in 0.9% Sodium Chloride Injection (500mL)	0264-9872-10	01935933

B. Braun Medical Inc. began recalling the lots on March 21, 2008 as a precautionary measure. This product recall was initiated due to a notification received from the supplier, Scientific Protein Laboratories (SPL), disclosing that one lot of Heparin Sodium, USP Active Pharmaceutical Ingredient acquired by B. Braun Medical Inc. has a heparin-like contaminant. To date, B. Braun Medical Inc. has not received any adverse event reports related to this issue.

The Food and Drug Administration has received reports of serious injuries and/or deaths in patients who have been administered Heparin injectable products of other companies containing this contaminant. As indicated in the notification issued by the supplier SPL, typical symptoms include anaphylactic-like reactions such as low blood pressure, shortness of breath, nausea, vomiting, diarrhea and abdominal pain.

Adverse reactions or quality problems experienced in the U.S. with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online:** www.fda.gov/medwatch/report.htm
- **Regular Mail:** use postage-paid FDA form 3500 available at: www.fda.gov/MedWatch/getforms.htm. Mail to MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787
- **Fax:** 1-800-FDA-0178

Adverse reactions or quality problems experienced in Canada with use of this product may be reported to Health Canada. For details on how to report these reactions please refer to the following website:

- **Online:** http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index_e.html

Customers who have product in their possession from the recalled product lots should discontinue use immediately. Patients reporting any problems that may be related to the use of this product should be advised to contact a physician. Customers may contact B. Braun Medical Inc. Customer Support Department at (800) 227-2862 for U.S. and (800) 624-2920 for Canada, Monday through Friday, 8 AM to 7 PM EST for instructions for handling the affected product and to arrange for replacement product.

#

RSS Feed for FDA Recalls Information [what's this?]

■ Sign up for Recall email updates.

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff

U.S. Food and Drug Administration

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

Covidien Initiates Voluntary Recall of Pre-Filled Syringes Containing Heparin

Contact:
Eric Kraus
508-261-8305

FOR IMMEDIATE RELEASE -- MANSFIELD, Massachusetts – March 28, 2008 - Covidien, formerly Tyco Healthcare, was recently notified by its supplier, Scientific Protein Laboratories LLC (SPL), of a nation-wide recall of Heparin Sodium USP active pharmaceutical ingredient. The voluntary recall affects the following 32 lots manufactured and distributed by Covidien in the United States.

Product	Lot Numbers
REF # 8881580121 Monoject PreFillTM 10U/mL Heparin Lock Flush Syringe, 10mL	7082274 7113214
REF # 8881580123 Monoject PreFillTM 10U/mL Heparin Lock Flush Syringe, 3mL	7051524 7113214
REF # 8881580125 Monoject PreFillTM 10U/mL Heparin Lock Flush Syringe 5mL	7051524 7082274 7113164 7113174
REF # 8881580300 Monoject PreFillTM 10U/mL Heparin Lock Flush Syringe 2.5mL in 3mL syringe	7051444
REF # 8881581125 Monoject PreFillTM 10U/mL Heparin Lock Flush Syringe 5mL, with BLUNTIP plastic cannula	7082274
REF # 8881590121 Monoject PreFillTM 100U/mL Heparin Lock Flush Syringe 10mL	7113064
REF # 8881590123 Monoject PreFillTM 100U/mL Heparin Lock Flush Syringe 3mL	7041194 7072154 7113034 8010194
REF # 8881590125 Monoject PreFillTM 100U/mL Heparin Lock Flush Syringe 5mL	7041194 7102804 7041204 7113034 7051534 7113044 7051544 7113054 7051554 7113104 7071924 7113114 7072034 7113154 7072044 8010064 7072054 8010114 7072064

	8010134 7072154 8010174 7082284
REF # 8881591125 Monoject PreFillTM 100U/mL Heparin Lock Flush Syringe 5mL, with BLUNTIP plastic cannula	7082284

Covidien began recalling the lots today as a precautionary measure. This product recall was initiated due to a notification received from the supplier, SPL, disclosing that two lots of Heparin Sodium USP Active Pharmaceutical Ingredient acquired by Covidien had a heparin-like contaminant. To date, Covidien has not received any adverse event reports related to this issue. Although a very small product line for Covidien, the Company is committed to following the direction of the Food and Drug Administration (FDA) regarding this matter.

The FDA has received reports of serious injuries and/or deaths in patients who have been administered Heparin injectable products of other companies containing this contaminant. As indicated in the notification issued by the supplier SPL, typical symptoms include anaphylactic-like reactions such as low blood pressure, shortness of breath, nausea, vomiting, diarrhea and abdominal pain.

Adverse reactions or quality problems experienced in the U.S. with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Online: www.fda.gov/medwatch/report.htm
- Regular Mail: use postage-paid FDA form 3500 available at: www.fda.gov/MedWatch/getforms.htm. Mail to: MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: 1-800-FDA-0178

Customers who have product in their possession from the recalled product lots should discontinue use immediately. Patients reporting any problems that may be related to the use of this product should be advised to contact a physician. Customers with questions about the return of recalled product should contact the Return Coordinator at 1-800-346-7197, ext. 8677, between 8:30am – 5:00pm (ET), Monday through Friday.

#

RSS Feed for FDA Recalls Information [what's this?]

Sign up for Recall email updates.

FDA Newsroom

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility

FDA Website Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

APR 21 2008

Warning Letter

Via FedEx and facsimile

WL: 320-08-01

Dr. Yan Wang, Ph.D.
General Manager
Changzhou SPL Company, Ltd (a/k/a "Kaipu")
3 Changhong West Road
Hutang Township, Wujin City
Changzhou
China

Dear Dr. Wang:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your active pharmaceutical ingredient manufacturing facility in Wujin City, Changzhou, China by U.S. Food and Drug Administration ("FDA") Investigator Regina T. Brown and Chemist Zi Qiang Gu on 20-26 February 2008. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) in the manufacture of active pharmaceutical ingredients (API). These deviations were listed on an Inspectional Observations form (FDA-483) issued to you at the close of the inspection.

These CGMP deviations cause your API to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)]. This section of the Act states that drugs, as defined in the Act, are adulterated when the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drugs meet the requirements of this Act as to safety and have the identity and strength and meet the quality and purity characteristics, which they purport or are represented to possess.

Our review included your March 17, 2008 and April 15, 2008 written responses to the FDA-483 observations. We note that some corrections appear to have been implemented and that you have promised that others will soon be implemented. However, your response does not adequately address some of the deficiencies, as further discussed below. Specific areas of concern include, but are not limited to:

1. **There is no assurance that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities.**

Our inspection disclosed that your firm lacked an adequate evaluation of the effectiveness of critical processing steps designed to remove impurities, and critical process parameters were not well defined or controlled (observation #1 of the FDA-483). The inspection also found that an impurity profile has not been established for the heparin sodium API (observation #2 of the FDA-483).

In your March 17, 2008, response to observation #1, you state that the firm has conducted two successful process validation studies, one in 2002 and one in 2004. However, the validation studies failed to determine whether the process was capable of adequately removing identified and unidentified impurities. Your response does not include data to demonstrate that your process will consistently remove impurities, and your firm continues to lack established impurity limits for the API. It is essential that your firm establish that controls are in place for assuring the consistent performance of the processing steps to remove impurities in order to ensure the identity, quality and purity of the drugs your firm produces.

In your response, your firm acknowledges certain deficiencies in providing evaluations of critical processing steps. Please provide data from validation studies that assess whether the process is capable of consistently removing impurities, and your evaluation of the reliability of the controls used to establish and monitor performance of the processing steps.

In your March 17, 2008, response to observation #2, you state that the current testing regimen for heparin sodium is consistent with industry practice reflected in the ICH Q7A Guidance (Laboratory Controls, Testing of Intermediates and APIs) which states that "Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin." Although a full impurity profile may not be necessary as part of the batch-to-batch testing of certain APIs, it is necessary that specifications for impurities be established for the production of all API and that each API batch be tested for conformance to these specifications. The ICH Q7A Guidance (Laboratory Controls, General Controls) states that appropriate specifications should be established for APIs, including for control of impurities. Your firm failed to establish appropriate specifications for identified and unidentified impurities for the heparin sodium API. Your firm also failed to perform adequate tests to detect impurities in this API.

In your March 17, 2008, response to observation #2 your firm also states that the complexity of the investigation into the recent heparin product recalls demonstrates the difficulty of isolating and identifying impurities in heparin due to the nature of the [ ] mixture of [ ] However, the mere fact that it is difficult to isolate and identify impurities is insufficient rationale for not establishing appropriate specifications for, and routinely monitoring, impurities during production. In fact, we note that you committed in your response to include an "impurity profile update" in each DMF annual report.

Please note that it is essential for your firm to establish appropriate specifications and adequate testing to ensure the consistent removal of undesirable impurities, including those that are potentially harmful to human health.

It is your responsibility to ensure that your API meets the identity, quality and purity characteristics that it is represented to possess.

2. **You fail to have adequate systems for evaluating the suppliers of heparin crude materials, and the crude materials themselves, to ensure that these materials are acceptable for use.**

Our inspection found (Observation #6 of the FDA-483) that you received lots of material from an unacceptable workshop vendor that were used in your API. In your March 17, 2008, response to observation #6, your firm acknowledges inadequacies in the firm's supplier qualification efforts. For example, you state that the firm received and used heparin crude materials from a workshop that had been designated by your firm in a "pre-audit" as "unacceptable" and that was ultimately not approved by your firm. Your firm used this crude material in the production of API lots that were shipped to the United States.

Your system for evaluating suppliers of crude heparin material is ineffective to ensure that materials are acceptable for use. As described above, your firm accepted and used heparin crude material from a supplier that you had preliminarily determined was unacceptable. Your system failed to verify that the supplier was acceptable prior to the use of the crude material. Furthermore, after your firm determined that the supplier was not acceptable, your firm failed to take any corrective action with respect to the processed raw material.

All raw materials that are received and used in producing heparin sodium API should be qualified using a system to ensure that raw materials are of acceptable identity, quality and purity before use. It is important to establish appropriate specifications for these materials and to assure your suppliers provide materials meeting these specifications. These specifications should be approved by the quality unit. Your firm has failed to establish appropriate specifications for your incoming crude materials.

Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.

3. **The test methods performed for heparin sodium USP have not been verified to ensure suitability under actual conditions of use.**

Our inspection found (Observation #4 of the FDA-483) that you have not ensured that certain USP compendial test methods were verified under actual conditions of use. Specifically, you have failed to conduct adequate verification of USP compendial test methods as applied to the production of your firm's API. The data you provided in your March 17, 2008, response did not include information about the suitability, accuracy, and detection limits of certain test methods for API, such as the protein test method, used by your firm. There was no indication from these data that your firm's test methods could reliably detect and quantify the presence of proteins in the finished API. In addition, your firm had not conducted suitability testing of the method to determine the limit of detection for the method. The suitability for use of the protein method for in-process testing was also not established.

In your March 17, 2008, response to the FDA-483, you state that the firm has conducted suitability tests. In addition, you state that the test method was not verified because it was a basic compendial test. You assert that USP <1226>, Verification of Compendial Procedures, states that verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. In your response, you also state that the laboratory performed basic suitability testing on the heparin sodium API analytical method in accordance with your standard operating procedures (SOPs).

We disagree with your assertions that verification is not required for those USP test methods used by your firm. In accordance with cGMP, analytical methods should be validated unless the methods used are included in a relevant pharmacopoeia or other recognized standard reference. If the method is a compendial method, verification of the methods should be conducted to determine that the method is suitable for its intended use under actual conditions. We acknowledge that the USP informational chapter <1226> suggests that there is a lesser need for verification for the simplest tests such as loss on drying, residue on ignition, and pH measurements. However, these do not include the test methods at issue, including the protein test method.

Further, the ICH Q7A guidance (Good Manufacturing Practices for Active Pharmaceutical Ingredients) at section 12.8 "Validation of Analytical Methods" states clearly that "the suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented." Thus, although it is not necessary to validate USP test methods, it is necessary to verify that these USP methods are suitable for the specific conditions of use. Furthermore, the suitability tests you describe in your response do not verify that the USP tests are suitable for the specific conditions of use.

Please provide data that demonstrate that the compendial test method has been verified and determined to be suitable under actual conditions of use.

4. **Equipment used to manufacture heparin sodium USP is unsuitable for its intended use.**

Our inspection team observed (Observation #7 of the FDA-483) that equipment tanks used in the final [redacted] step were constructed of [redacted] These tanks were identified as clean. However, unidentified material was observed adhering to the inside surfaces of tanks. It was also observed that surfaces of the tank were scratched, not smooth. We also note that volume markings on the outside of the [redacted] tanks had tape adhered to it with markings. In addition, the cleaning method used for cleaning these tanks was not qualified.

There should be written procedures for cleaning of equipment. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Acceptance criteria should be established and cleaning procedures should be defined and evaluated.

In your response to observation #7, you stated that the [redacted] tanks used in the final [redacted] step will be replaced with [redacted] This [redacted] will be equipped with clean-in-place system and an automated level reader. Until the new tanks arrive, you state that you will replace the existing [redacted] tanks with new [redacted] tanks and conduct cleaning validation on the new tanks using the manual cleaning methods after each cleaning.

Please provide data that show how the [redacted] tanks are qualified and the cleaning procedures are validated.

Your corrective action to replace [redacted] tanks with [redacted] is noted. However, it is your responsibility to ensure that equipment used to process heparin sodium does not meaningfully alter quality of the API by being additive, reactive or absorptive.

Once you have installed and qualified the [redacted] please provide information on equipment qualification and cleaning validation for these tanks.

The inspectional observations listed on the FDA-483 and the concerns described above indicate significant deficiencies in your overall quality system. An effective quality system must assure that a firm's manufacturing operations are adequate and that the API meets its established specifications for identity, quality and purity. There should be a quality unit that is independent of production and capably discharges quality assurance and quality control responsibilities. Please respond to the FDA with your corrective action plan to address the above concerns with respect to your quality system.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMP that exist at a firm. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practice.

Shipments of articles manufactured by your firm are subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C Act [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. 351(a)(2)(B)]. Until all corrections have been completed and FDA can confirm compliance with CGMP, this office will continue to recommend disapproval of any new applications or supplements listing your firm as the manufacturer of active pharmaceutical ingredients.

Please respond to this letter in English (including attachments) within 30 days of receipt and identify your response with FEI# 3003335664. Any future shipments of API manufactured at your 3 Changhong West Road site will be refused admission into the United States.

Please contact Anthony A. Charity, Compliance Officer, at the address and telephone numbers shown below, if you have any questions or concerns regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue, Bldg 51, Room 3246
Silver Spring, MD 20993
Tel: (301) 796-3191; FAX (301) 847-8741

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigation, HFC-134, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Preapproval Inspection Priorities

1. New molecular entities (NMEs) (includes finished drug product and the active pharmaceutical ingredient)
2. Priority NDAs
3. First application filed by an applicant
4. For-Cause inspection
5. For original applications, if the current CGMP status is unacceptable or greater than 2 years
6. For Certain pre-approval supplements, such as site change or major construction, if the CGMP status is unacceptable
7. Treatment IND inspections
8. Information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients

Source: FDA Compliance Program Guidance Manual

Number of Deaths of Patients Receiving Heparin Reported to FDA, January 1, 2007 through April 13, 2008

Month the Medical Event(s) Occurred	Number of Reported Deaths*	Reported Deaths with One or More Allergic/Hypotensive Symptom(s)
Jan-07	3	1
Feb-07	1	0
Mar-07	4	2
Apr-07	4	2
May-07	2	1
Jun-07	3	2
Jul-07	4	2
Aug-07	1	1
Sep-07	2	2
Oct-07	7	4
Nov-07	**11**	**10**
Dec-07	**20**	**13**
Jan-08	**31**	**21**
Feb-08	**28**	**18**
Mar-08	3	0
Unknown date	7	2
Total	131	81

Monday, February 11, 2008 3:46 PM

Subject: FDA MedWatch - Heparin Sodium Injection - Serious Adverse Events Reported In Patients Receiving Bolus Doses Of Medication

MEDWATCH **The FDA Safety Information and Adverse Event Reporting Program**

FDA informed healthcare professionals of important warnings and instructions for Heparin Sodium Injection use. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension. Most events developed within minutes of heparin initiation although the possibility for a delayed response has not been excluded. The reports have largely involved use of multiple-dose vials. However, there have been several cases in which product from multiple, single-dose vials have been combined to administer a bolus dose. Heparin sodium is an anticoagulant (blood thinner) that is used in patients undergoing kidney dialysis, certain types of cardiac surgery, and treatment or prevention of other serious medical conditions, including deep venous thrombosis and pulmonary emboli. Heparin treatment is initiated using high doses (5000-50,000 units) given directly into the blood stream (intravenously) as a bolus. Serious adverse events have recently been reported in patients who received these higher bolus doses.

The manufacture of multiple-dose vials of heparin sodium has been suspended pending the completion of an extensive ongoing investigation to determine the root cause of the problem. Because heparin sodium is a medically necessary product and serious public health consequences would result if there were a sudden shortage of the drug, the multiple-dose vials of heparin sodium manufactured by Baxter that are currently in distribution will not be recalled. See the FDA Public Health Advisory for Agency recommendations to healthcare professionals on the use of heparin sodium for injection.

Read the complete 2008 MedWatch Safety Summary including a link to the FDA Public Health Advisory, Q & A Document, and News Release regarding this issue at:
http://www.fda.gov/medwatch/safety/2008/safety08.htm#HeparinInj2

THE WALL STREET JOURNAL. ONLINE

February 15, 2008

FORMAT FOR PRINTING sponsored by TOSHIBA Leading Innovation

Heparin Probe Finds U.S. Tie to Chinese Plant

By THOMAS M. BURTON, ANNA WILDE MATHEWS, NICHOLAS ZAMISKA and GORDON FAIRCLOUGH
February 15, 2008; Page B1

DOW JONES REPRINTS

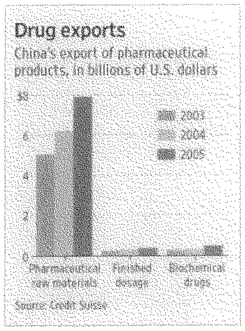
This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues, clients or customers, use the Order Reprints tool at the bottom of any article or visit: www.djreprints.com.

- See a sample reprint in PDF format.
- Order a reprint of this article now.

Baxter International Inc.'s investigation into the cause of deaths and allergic reactions linked to its blood-thinner heparin is focusing on variations in batches of the active ingredient for the drug, most of which were supplied by a Chinese manufacturing facility co-owned by a Wisconsin company.

Baxter said the active ingredient for its heparin was supplied by Scientific Protein Laboratories LLC, a Waunakee, Wis., company with a manufacturing facility there and a joint-venture operation called Changzhou SPL in Changzhou, China. Baxter declined to elaborate on the nature of the variations, but heparin is a particularly tricky product to manufacture because it is derived from pig intestines.

David G. Strunce, president of Scientific Protein, said most of its active ingredient for heparin is made at the China plant, but some comes from the Wisconsin facility. "There's nothing that would explain these reactions, and we are very concerned about this," he said. "We have no idea if these reactions have anything to do with our product."


Drug exports

China's export of pharmaceutical products, in billions of U.S. dollars

Source: Credit Suisse

Though the cause of the reactions still isn't clear, the incident places Baxter and Scientific Protein, which is majority-owned by the Bethesda, Md., buyout firm **American Capital Strategies** Ltd., at the center of a broader debate about the oversight of overseas drug manufacturing. The U.S. Food and Drug Administration has said it didn't inspect the Chinese operation, which is also owned by Changzhou Techpool Pharmaceutical Co., of China.

On Monday, Baxter said it had temporarily stopped production of heparin because of about 350 bad reactions, including four fatalities, potentially tied to the drug, which is used primarily in kidney dialysis and heart surgery. An FDA official estimated that about 40% of the adverse reactions among patients taking the Baxter drug were classified as serious. They ranged from stomach pain to vomiting and diarrhea, low blood pressure, speeding heartbeats and fainting.

China's rise to become the world's largest manufacturer of drug ingredients has helped drug companies elsewhere trim production costs, particularly for generic products like heparin, where margins are generally slim. Changzhou SPL, also known by its Chinese name, Kaipu Biochemical Co., is one of hundreds of Chinese manufacturers that have quietly become a linchpin of the global pharmaceutical industry. In 2005, China had $4.4 billion, or 14%, of the world's $31 billion market for active pharmaceutical ingredients, topping India and Italy, according to a report written last year by Jinsong Du, a health-care analyst in Hong Kong with Credit Suisse.

Yesterday, Sen. Charles Grassley, an Iowa Republican, wrote to the FDA and to Baxter, asking for more data about the heparin and its supplier. Michigan Democrats John Dingell and Bart Stupak, leaders of the House Energy and Commerce Committee, have been investigating import-safety issues with drugs and medical devices. In their own letter to the FDA, they said "American lives are unnecessarily being placed at risk" by the limited oversight over foreign manufacturing.

Baxter spokeswoman Erin Gardiner said the company is using "molecular separation" analysis to "look for chemically meaningful differences" between heparin batches linked to bad reactions and "control" batches known to be of high quality.

Heparin is a complex sugar molecule that normally exists on the lining of blood vessels in people and animals. It is now made from pig intestines, but processing them can lead to impurities. "Crushing tissue to get extracts means you can get contamination from other things in the tissue," says John R. Hess, a blood expert at the University of Maryland.

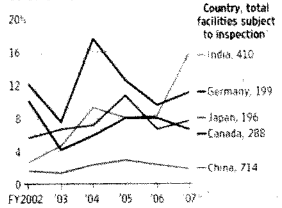
In manufacturing, raw intestines are exposed to an enzyme and then to a resin that separates the heparin from the rest of the liquid. The end product is heat-treated to destroy microorganisms.

Scientific Protein Laboratories said that the cause of the patient reactions hasn't been identified. The company said that it has been making the heparin active ingredient at the Chinese facility since 2004, and that it "engages in the same testing and quality-control procedures as U.S. facilities that produce bulk heparin" and meet FDA standards. American Capital Strategies didn't return calls.

An FDA spokeswoman said the agency is "doing everything possible to discover the root cause of these reactions, but this information takes time to gather." Neither the Chinese State Food and Drug Administration nor the General Administration for Quality Supervision, Inspection and Quarantine, which polices quality issues, could be reached. Changzhou Techpool declined to comment.

Lack of Oversight

Percentage of facilities involved in the manufacture of drugs for the U.S. market that were inspected by the FDA, selected countries



[1] Data supplied on Sept. 26, prior to the end of the fiscal year, Sept. 30 [2] Based on the number of facilities the FDA used to plan its 2007 prioritized surveillance inspections

Source: Government Accountability Office analysis of FDA data

Yesterday at Changzhou SPL's factory, about a two-hour drive northwest of Shanghai, the smell of chemical reagents and the whir of exhaust fans were detectable outside. Two workers in green uniforms, black rubber boots, face masks and surgical caps scrubbed equipment outside the plant. Guards blocked reporters from entering the compound.

U.S. regulators can provide only limited oversight for such operations. A woman in the administration office of Changzhou SPL said the company is expecting investigators from the U.S. FDA to arrive Monday for their first visit to the plant. "We'll fully cooperate with Baxter and FDA investigators," said a manager of the quality-control department.

The FDA isn't legally required to inspect every foreign drug facility, but it generally does examine them if they are named as a maker in a new application to market a drug in the U.S. If the holder of an existing, approved application switches manufacturers, the new facility would usually get inspected as well. However, a legal requirement for drug manufacturers to get inspected every two years applies only to domestic plants, not the growing list of overseas facilities.

The FDA's commissioner, Andrew von Eschenbach, has said he would like to base FDA inspectors and other experts overseas, including in China. Currently, they are all in the U.S. and must do overseas inspections during strenuous trips that typically allow the foreign drug makers to have advance notice. The agency said an FDA presence in China would require formal agreement from the host nation, and the State Department "is presently discussing this with the Foreign Ministry on behalf of the FDA and the U.S. government."

--Ellen Zhu and Sue Feng contributed to this article.

Write to Thomas M. Burton at tom.burton@wsj.com[1], Anna Wilde Mathews at anna.mathews@wsj.com[2], Nicholas Zamiska at nicholas.zamiska@wsj.com[3] and Gordon Fairclough at gordon.fairclough@wsj.com[4]

URL for this article:
http://online.wsj.com/article/SB120302351904669441.html

Hyperlinks in this Article:
(1) mailto:tom.burton@wsj.com
(2) mailto:anna.mathews@wsj.com
(3) mailto:nicholas.zamiska@wsj.com
(4) mailto:gordon.fairclough@wsj.com

Copyright 2008 Dow Jones & Company, Inc. All Rights Reserved

This copy is for your personal, non-commercial use only. Distribution and use of this material are governed by our **Subscriber Agreement** and by copyright law. For non-personal use or to order multiple copies, please contact Dow Jones Reprints at 1-800-843-0008 or visit **www.djreprints.com**.

RELATED ARTICLES AND BLOGS

Related Articles from the Online Journal

- Two U.S. Goals Collide: Free Trade, Security
- A Chinese Facility Made Much Of Active Ingredient in Heparin
- Baxter Halts Heparin Production Amid Reports of Allergic Reactions
- Baxter Issues Heparin Recall

Blog Posts About This Topic

- Is there a Chinese connection with the recalled heparin? omniphysicians.com
- China Plant Produced Key Ingredient for Baxter's Heparin blogs.wsj.com

More related content *Powered by Sphere*

Hello Visitor Register Sign-in

LAT Home My LATimes Print Edition All Sections

Jobs | **Cars.com** **Real Estate** | **More Classifieds**

Los Angeles Times Business

☐ SEARCH

You are here: LAT Home > **Business News**

Business

- Advertising
- Autos
- The Biz
- Money
- Real Estate
- Small Business
- Technology
- Video Games
- Work & Careers

Business Tools:

- Investor Tips
- Law Resources
- Money Library
- Money Q & A
- Bank Rates
- Press Releases

News

California | Local
National
World
Entertainment
Business
Sports
Campaign '08
Science
Environment
Opinion
Columnists
Print Edition
Readers' Rep
Corrections

Calendarlive
The Guide
The Envelope
Travel
Magazine
Home & Garden
Health
Food
Autos
Books
Image
Arts & Culture
Living Green
Video
Photography
Obituaries
Crossword, Sudoku
Your Scene
Blogs
All Sections

Buy, Sell & More

Jobs
Cars
Real Estate
Apartments
Personals

TRADE

Plant in China under scrutiny

Initial testing finds irregularities with blood thinner heparin made at the facility.

By Don Lee and Ricardo Alonso-Zaldivar, Los Angeles Times Staff Writers
February 20, 2008

CHANGZHOU, CHINA -- The maker of a blood thinner suspected in four U.S. deaths and allergic reactions in 350 people said Tuesday that its investigation was focusing more closely on whether something went awry during the processing of ingredients in China.

Baxter Healthcare Corp. spokeswoman Erin Gardiner said testing had detected irregularities in samples of the drug, heparin, that were processed in China from raw material extracted in China. No such irregularities were detected in heparin made from raw materials from China but processed at a supplier's plant in Wisconsin. Gardiner stressed that the findings were preliminary and that the company had reached no final conclusions about what caused the adverse reactions among patients.

Baxter has said that a Chinese plant here, Changzhou SPL, was the source of much of the active ingredient in its heparin. The U.S. Food and Drug Administration said it never inspected the factory because the agency mixed up the company with another one that has a similar name. Changzhou SPL apparently wasn't examined by Chinese drug regulators either, because it isn't licensed as a pharmaceutical manufacturer with the Chinese government.

Such bureaucratic oversights are of growing concern in the U.S., given that China accounts for about 22% of the foreign factories producing drugs for the American market -- more than any other single country. Yet facilities in China accounted for only 6% of the overseas inspections conducted by the FDA from 2002 to 2007.

A report by the Government Accountability Office last fall found that the FDA conducted 88 inspections in China during the five-year period, from a low of nine in 2003 to 21 in 2005. That means the vast majority of the 714 Chinese facilities involved in making drugs for the U.S. market were not inspected. By contrast, Italy, with 150 manufacturing facilities, underwent 131 inspections over the five years.

The FDA has said it would inspect the Chinese factory that was the source of Baxter's heparin this week but didn't specify when.

Heparin is derived from pig intestines, and China has come to dominate the global market thanks to its abundant supply of swine and low labor costs. The country exported more than $100 million worth of heparin ingredients last year, according to various estimates.

Changzhou SPL -- a joint venture that is 55% owned by a Wisconsin company and 45% by a Chinese partner -- was China's sixth-largest exporter of heparin ingredients last year by volume. On Tuesday, Changzhou SPL maintained its silence. Employees and guards at the plant, located amid farmlands on the edge of this dusty city west of Shanghai, refused to comment.

But about 10 miles to the north, another leading maker of heparin ingredients welcomed a reporter to tour its facility and ask questions. Managers at Changzhou Qianhong Bio-pharma Co., China's second-largest exporter of heparin, provided copies of certificates from regulators in China and Europe, its primary export market. They showed fingerprint-scanners at entrances, labs and clean rooms.

Chen Honglei, Qianhong's export manager and an 18-year industry veteran, said that he hadn't been inside Changzhou SPL's operations but that the production processes at the major heparin ingredient manufacturers in China were similar. He added that SPL had an experienced team led by Wang Yan, who came from SPL's American owner, Scientific Protein Laboratories of Waunakee, Wis., which has been making heparin's active ingredient in the U.S. for three decades.

Email ✉ | Print 🖶 | Text ⊕

More Business News

- Microsoft threatens to turn Yahoo bid hostile
- Finding the right investment mix in a tumultuous market
- Few places to hide from downturn

Most Viewed | Most E-mailed | Related News

Deals at Local Stores
Coupons
Newspaper Ads

Place an Ad

In the Newspaper
Online

Settings & Services

Sign In
Register
Personalized News
E-Mail Newsletters
RSS Feeds
Help
Contact Us
L.A. Times Archives
Reprint Requests
Work for Us

Home Delivery

Customer Support
Subscribe

Changzhou SPL "is quite well known. It enjoys a good reputation," Chen said.

Yet like most everybody else in the industry, Chen was puzzled why that plant wasn't licensed with the Chinese drug regulatory agency. According to China's State Food and Drug Administration database, 32 companies are registered to produce heparin compounds.

"That company is not a pharmaceutical manufacturer, so it has no license,' State FDA spokesman Shen Chen said of Changzhou SPL. He declined to comment further. The agency has yet to release any information on the matter.

Licensed pharmaceutical plants in China say Chinese regulators have typically visited at least once a year, although that has increased in recent months as China's drug and food safety practices came under global scrutiny after recalls and product scares involving Chinese-made medicine, toys and pet food. Changzhou Qianhong, for example, said it was inspected three times last year, twice unannounced.

Usually the FDA will make an on-site visit before a new foreign drug or active ingredient maker is allowed in, but the mistake with Changzhou SPL has drawn fire from members of Congress. Changzhou SPL started operations in 2004.

The FDA says it is aware of only one other Chinese company that ships the active ingredient for heparin to U.S. pharmaceutical makers that produce and sell the finished drug. That company, Shenzhen Hepalink Pharmaceutical Co., said the FDA inspected its facility several years ago before issuing a certificate for sales to the U.S.

Shenzhen Hepalink, China's largest exporter of active ingredients for heparin, is a supplier to Baxter's Illinois rival, APP Pharmaceuticals Inc.

Chinese producers of heparin ingredients have been exporting to Europe for two decades and to the U.S. for several years. Shipments have grown briskly, although the volume shrank last year because a shortage of pigs led to a sharp increase in prices. Intestines from about 3,500 pigs are needed to make about 2.2 pounds of active ingredient for injectable heparin.

There are no squealing pigs at Changzhou Qianhong's sprawling facility. Rather, shipments of extracted ingredients in granule form come into Qianhong's operation, where impurities are removed.

Jiang Wenqun, Qianhong's deputy general manager, said the company spent about $17 million to build a 22,000-square-foot active ingredient plant, which began operations four years ago. The private firm, which employs about 260 people and also makes finished heparin and other compounds, has been exporting since 1991. Last year, she said, its revenue surpassed $42 million, with a little more than half of that coming from heparin exports.

Managers at Qianhong said the investigation of the Baxter drug hasn't hurt sales, although their European clients have called asking about the matter. "I'm not worried," said Chen, Qianhong's export manager. "After all, this is a very old product. We've been producing it for decades."

don.lee@latimes.com

ricardo.alonso-zaldivar

@latimes.com

Lee reported from Changzhou and Alonso-Zaldivar from Washington.

Save over 50% off the newsstand price. Subscribe to The Times now!

Coordinated celebs
In Tinseltown, matching outfits counts. Here are some dual dressing examples, both good and bad. **Photos**

View our readers' photos of **Hillary Clinton** and share your own at ***Your Scene.***

Submit your photo or video >>

THE WALL STREET JOURNAL.
HEALTH BLOG

February 27, 2008, 8:46 am

China Washes Hands on Heparin Purity

Posted by Jacob Goldstein

If the U.S. is concerned about the quality of raw heparin imported from China, the Americans need to make sure the proper controls are in place, China's State Food and Drug Administration said today.

Associated Press

The Chinese FDA said it works with foreign regulators to monitor factories, but the ultimate responsibility for "safeguarding the legality, quality and safety of active pharmaceutical ingredients" lies with the importing nation, the WSJ's Gordon Fairclough reports.

A version of the blood thinner heparin, sold by Baxter International, has been associated with illnesses and deaths in this country. Some of the key raw ingredient for the drug comes from China. In today's statement, China's FDA put concerns about the Chinese product at arm's length, noting that the Chinese manufacturer that supplied the raw heparin is majority U.S. owned, its production technology was supplied by an American firm and all of its output was exported to the U.S.

Chinese producers of active pharmaceutical ingredients must be drug companies that are "registered and certified" by the Chinese FDA, an agency spokeswoman told the WSJ. Foreign buyers should confirm this certification and importing countries "should make strict tests" on ingredients. The company that sold the raw heparin used by Baxter wasn't certified by the Chinese FDA because it was registered as a chemical company, not a drug company.

Permalink | Trackback URL: http://blogs.wsj.com/health/2008/02/27/china-washes-hands-on-heparin-purity/?mod=WSJBlog/trackback/
Save & Share: Share on Facebook | Del.icio.us | Digg this | Email This | Print
Read more: Drugs

Hello Visitor Register Sign-In

LAT Home : My LATimes : Print Edition : All Sections

Jobs . Cars.com Real Estate | More Classifieds

Los Angeles Times National

SEARCH

You are here: LAT Home > **National News**

National

» Washington

News

California | Local
National
World
Entertainment
Business
Sports
Campaign '08
Science
Environment
Opinion
Columnists
Print Edition
Readers' Rep
Corrections

The Guide
The Envelope
Travel
Magazine
Home & Garden
Health
Food
Autos
Books
Image
Arts & Culture
Living Green
Video
Photography
Obituaries
Crossword, Sudoku
Your Scene
Blogs
All Sections

Buy, Sell & More

Jobs
Cars
Real Estate
Apartments
Personals
Deals at Local Stores
Coupons
Newspaper Ads

Place an Ad

In the Newspaper
Online

Settings & Services

Sign In
Register
Personalized News
E-Mail Newsletters
RSS Feeds
Help

Look-alike drug may have tainted heparin

The FDA wants to know if contamination of the blood thinner occurred in the U.S. or China and whether it was deliberate.

By Ricardo Alonso- Zaldivar, Los Angeles Times Staff Writer
March 6, 2008

WASHINGTON -- A recalled blood thinner made with active ingredients from China appears to have been contaminated by a mysterious look-alike substance, now the focus of an investigation into as many as 19 U.S. deaths and nearly 800 serious drug reactions, federal officials said Wednesday.

The drug -- heparin -- is a generic medication given to prevent blood clots. The manufacturer, Illinois-based Baxter Healthcare Corp., issued recalls last month after it noticed an unusual increase in reports of severe side effects.

The Food and Drug Administration's findings raised questions about whether the medication was deliberately contaminated or whether some problem occurred in processing, either in China or in the United States.

FDA officials said the as-yet unidentified contaminant was detected only through sophisticated testing not generally done by manufacturers or their suppliers. In the kinds of routine tests required before the drug was shipped, the contaminant apparently behaved much like heparin, and its presence went unnoticed.

"This substance . . . appears to act like heparin," said FDA Deputy Commissioner Janet Woodcock, calling the case "a classic chemical investigation."

A case of deliberate contamination would echo last year's massive pet food recall, prompted by a chemical that a supplier in China mixed with food to boost the product's performance in nutritional testing.

FDA officials cautioned that the investigation was at an early stage and that they were still seeking answers to many basic questions. Indeed, investigators have yet to establish whether the suspect ingredient actually caused the severe reactions -- including life-threatening drops in blood pressure -- seen in some patients.

"There is an association between the contaminant and the presence of adverse events, but it is not a direct causal link yet," Woodcock said.

The agency has come under fire from Congress because it failed to inspect the Chinese facility that produced the heparin, Changzhou SPL, before allowing it to ship the drug to the United States. Someone at the FDA mixed up the name of the plant with that of another facility that had been inspected. A belated FDA inspection last month found a series of problems with documentation, equipment and waste disposal at the Changzhou plant.

Baxter said in a statement that it, too, is focusing on possible problems with the active ingredient. "The root cause may be associated with the crude heparin, sourced from China, or from the subsequent processing of that product before it reaches Baxter," the company said.

But Baxter's supplier, Scientific Protein Laboratories, said it was "premature" to single out the active ingredient supplied from China. Wisconsin-based Scientific Protein Laboratories and a Chinese company are joint-venture partners in the Changhzou plant.

"FDA speculated that the source of the adverse events may be a contaminant," the Wisconsin company's statement said. "It is important to note that this theory is speculation at this point."

The company, a well-established supplier of heparin, said it is fully cooperating with the

Email | Print | Text ⊞ | RSS

ADVERTISEMENT

Most Viewed Most E-mailed

1. Parents warned about sleeping with infants
2. McCain visits New Orleans' Lower 9th Ward
3. In the end, Lakers again blew away the Nuggets
4. Kobe is a 49er in Lakers victory
5. Lakers' Kobe Bryant is fit to be MVP
6. San Bernardino sheriff's deputy kills driver after pursuit
7. Pacino and De Niro: How the mighty have fallen
8. Ongoing Gypsy dispute may be motive in woman's death in firebombing
9. Sleeping with the enemy
10. Run on rice makes its way to U.S.

Headlines: World

1. Gap opens between Al Qaeda and allies
2. Sunni bloc ready to rejoin Iraq Cabinet
3. On his weekends, Chinese Samaritan saves lives
4. Petraeus promotion ensures future for Bush war policy
5. Iraq's 'King of Clubs' Ibrahim reportedly arrested

Latimes.com e-mails

Stay on top of the presidential campaign, the latest entertainment news or find something to do tonight. Sign up FREE!

Your Scene: Reader Photos

View our readers' photos of Weird America and share your own at Your Scene.
Submit your photo »

Contact Us
L.A. Times Archives
Reprint Requests
Work for Us

Home Delivery

Customer Support
Subscribe

FDA investigation.

Heparin is derived from a substance found in the lining of pigs' intestines. China dominates the world market because of its low labor costs and an abundant supply of pigs.

The Changzhou SPL plant gets its raw materials from middlemen known as consolidators, who deal with slaughterhouses that receive pigs from farms. China has recently instituted tighter veterinary controls, but it's unclear how far back U.S. investigators will be able to trace the sources of the heparin. Baxter said it relies on SPL to maintain the integrity of its supply chain.

Baxter said it started noticing an increase in reports of problems in late December. Initially, these reports came from dialysis centers; later, problems started to surface at hospitals. The company launched an internal investigation Jan. 4 and notified the FDA a week later.

Baxter officials said they were at first unsure of the scope of the problems and contacted the FDA as soon as they learned that patients in hospitals, and not just those in dialysis centers, were affected. Heparin, a powerful drug, can cause serious reactions even under normal circumstances.

But the company and the FDA disagree on the extent of the potential damage caused by the recalled heparin. Baxter says it has received about 450 reports of drug reactions and is investigating four deaths, none of which has been conclusively tied to its product.

The FDA says it has received 785 reports of serious reactions, including 19 deaths. Baxter is focusing on reports received since Dec. 15; the FDA is looking at all of 2007.

The FDA's Woodcock said the contaminant was detected at fairly high levels -- ranging from 5% to 20% -- in some of the samples tested by the agency. It appears to be a molecular cousin of heparin, although it has yet to be identified.

"We do not know whether it inadvertently got into the supply or was added," she said.

ricardo.alonso-zaldivar@ latimes.com

Save/Share

2008 Festival of Books
The 13th Annual Los Angeles Times Festival of Books, the country's largest celebration of the written word, kicks off this Saturday, April 26 at UCLA. Click here for complete details.

Autos A-Z
Find your next car or your dream car from Acura to Volvo.

ADS BY GOOGLE

Labia Plastic Surgery
View the Latest Offers & Save on Labia Plastic Surgery
SafeCompare.com/

Asian Eyelid Surgery
Asian plastic surgery specialist Charles S. Lee MD Board Certified
www.asiancosmeticsurgery.com

10 Rules Losing Belly Fat
I Fought To Lose Fat, with These 10 Rules I Lost 9 lbs every 11 Days.
www.FatLoss4Idiots.com

Awful Plastic Surgery
Your Online Source For Awful Plastic Surgery is here.
Pictures.NatureExhibit.org

Tummy Tuck Abdominoplasty
Plastic Surgeon Northern Virginia Dr. David Berman Cosmetic Surgeon
www.BermanCosmeticSurgery.com

THE WALL STREET JOURNAL. ONLINE

FORMAT FOR PRINTING sponsored by TOSHIBA Leading Innovation >>>

March 7, 2008

German Firm Recalls Heparin With China Link

Batches Had Ingredient From Different Source Than Baxter's Product

DOW JONES REPRINTS

This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues, clients or customers, use the Order Reprints tool at the bottom of any article or visit: www.djreprints.com.

- See a sample reprint in PDF format.
- Order a reprint of this article now.

By ANITA GREIL, ANNA WILDE MATHEWS and THOMAS M. BURTON
March 7, 2008; Page B4

A German company is recalling some batches of the blood thinner heparin that were made using an active ingredient from China, broadening the scope of safety worries about the widely used drug.

Rotexmedica GmbH Arzneimittelwerk didn't rely on the same active-ingredient supplier as **Baxter International** Inc., the maker of heparin that has been recalled in the U.S. But patients taking both of the recalled products suffered similar allergic-type reactions and incidents of low blood pressure.

- **The News:** A German company recalled some batches of the blood thinner heparin amid safety concerns.
- **Background:** Heparin previously had been recalled in the U.S. by Baxter International.
- **Unanswered Questions:** The FDA is continuing to investigate reports of allergic reactions to the drug.

It isn't clear what caused the reactions in the German patients who took the Rotexmedica heparin that is being recalled, or whether the problem is related to the Chinese manufacturers. About 80 patients who took heparin from the recalled Rotexmedica batches had the problems. No deaths from such reactions have been reported in German patients, according to the U.S. Food and Drug Administration.

Still, the disclosure of a Chinese link to another heparin recall may underscore concerns about oversight of the Chinese drug industry, and particularly its role as a major supplier of raw heparin, which is made from the intestines of pigs. The raw ingredient often emerges from a network of small workshops and other suppliers in China that get little, if any, regulatory oversight.

The FDA said that in the wake of the German report, it was asking all makers of finished heparin and the active heparin ingredient to run a new regimen of tests that would detect a contaminant that has been found in some batches of the Baxter heparin. The agency said it still hasn't identified the source or the identity of the substance, which wasn't picked up by standard tests done to check the drug's quality.

A document prepared by the German state of Schleswig-Holstein Department of Healthcare says the suppliers of the active ingredient for the three recalled Rotexmedia batches are Changzhou Qianhong Bio-Pharma Co. and Yantai Dongcheng Biochemicals Co. The document was sent to German pharmacists and doctors, along with a letter from Rotexmedica announcing the recall, Wednesday. The FDA publicly disclosed the German recall yesterday.

Employees in the foreign-trade and quality-control departments at Changzhou Qianhong Bio-Pharma said they were unaware of the recall or the German authorities' action.

Employees at the foreign-trade department of Yantai Dongcheng said representatives of the company were meeting with Chinese government officials Friday morning in China to discuss the matter.

Baxter's active ingredient was from Scientific Protein Laboratories LLC, which has a joint-venture Chinese manufacturing facility called Changzhou SPL. Baxter has said the contaminant in its drug was found in batches made using raw heparin from China. However, it isn't clear where or how the unknown substance got into the Baxter product.

Scientific Protein said the German recall "demonstrates that the heparin problem is not within Changzhou SPL's or Baxter's manufacturing facilities."

In its letter, Rotexmedica said there had been an "increased occurrence" of allergic-type reactions and low blood pressure in some patients taking medicine from the recalled lots, and "it can't be ruled out that the quality of the batches has been compromised."

Rotexmedica and German regulators couldn't be reached for comment.

The FDA said it wasn't clear that all of the German patients who had reactions had taken the Rotexmedica product. There was a cluster of reactions at a German dialysis center, the FDA said. The agency said there were fewer than 100 reports of reactions in German patients. The German state health-agency document used the figure of 80 reactions in connection with the recalled Rotexmedica batches.

In the U.S., the FDA has said it has 19 fatality reports that appear to involve the allergic type of reaction in patients taking heparin. It wasn't clear how many of them took the Baxter product, and the deaths have occurred since Jan. 1, 2007. The FDA said it has received a total of 785 reports of problems in patients who took some form of heparin, though it isn't clear that these are all related to drug reactions, and some may be duplicates.

–Ellen Zhu in Shanghai contributed to this article.

Write to Thomas M. Burton at tom.burton@wsj.com[1]

URL for this article:
http://online.wsj.com/article/SB120485991619318731.html

Hyperlinks in this Article:
(1) mailto:tom.burton@wsj.com

Copyright 2008 Dow Jones & Company, Inc. All Rights Reserved

This copy is for your personal, non-commercial use only. Distribution and use of this material are governed by our **Subscriber Agreement** and by copyright law. For non-personal use or to order multiple copies, please contact Dow Jones Reprints at 1-800-843-0008 or visit **www.djreprints.com**.

THE WALL STREET JOURNAL.
ONLINE

FORMAT FOR PRINTING sponsored by TOSHIBA Leading Innovation >>>

March 21, 2008 1:38 a.m. EDT

China Orders Tighter Controls On Production of Heparin

DOW JONES REPRINTS
This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues, clients or customers, use the Order Reprints tool at the bottom of any article or visit: www.djreprints.com.

- See a sample reprint in PDF format.
- Order a reprint of this article now.

Associated Press
March 21, 2008 1:38 a.m.

SHANGHAI, China -- In a reversal of its earlier stance, China's drug safety agency is ordering local authorities to tighten controls on production of heparin, a blood-thinner linked to 19 deaths in the U.S. and hundreds of allergic reactions.

The State Food and Drug Administration issued the order in a notice seen Friday on its Web site that requires heparin producers to obtain the raw chemicals used to make the drug from registered suppliers. Raw heparin suppliers, meanwhile, are required to improve their management and tests on their products, it said.

Earlier, the Chinese drug agency had insisted that ensuring the quality of exported chemicals like heparin was the responsibility of importers and importing countries.

Heparin is derived from a mucous obtained from pig intestines and other animal tissues, often processed by small, unregistered workshops. Investigations following the reports of sometimes fatal adverse reactions in the U.S., and of similar allergic reactions in Germany, prompted China's new crackdown on unlicensed production.

Earlier this week, the U.S. Food and Drug Administration identified the contaminant in heparin batches from a Chinese supplier to U.S. pharmaceuticals company Baxter International Inc. as oversulfated chondroitin sulfate. Baxter recalled nearly all its U.S.-sold heparin injections after some patients experienced extreme allergic reactions to the products. There have been similar recalls of Chinese-sourced heparin in Germany and Japan.

Drug safety officials say they haven't confirmed yet if the contaminant, which chemically mimics heparin, caused the dangerous allergic reactions. But both the U.S. and Chinese drug agencies said they were investigating how the oversulfated chondroitin sulfate, which does not occur naturally, got into the heparin batches.

The heparin probe, coming just a year after the toxic chemical melamine was found in a pet-food ingredient from China, has refocused attention on various problems with safety and quality of Chinese-made drugs, foods and other products.

China's drug agency has often failed to adequately regulate the country's medicine supplies, and an explosion of production capacity has resulted in numerous reports of adulterated, counterfeit and otherwise unsafe pharmaceuticals. Last year, China executed the drug agency's director for taking bribes to approve unqualified medicines.

China so far has not reported any adverse allergic reactions to heparin products used in the country. But the Chinese drug safety agency ordered heparin makers to closely monitor reactions to their products and immediately halt production and recall any products with safety problems.

Deerfield, Illinois-based Baxter International was buying its heparin through a Wisconsin-based producer, Scientific Protein Laboratories, or SPL, which in turn owns a Chinese factory, Changzhou SPL, and buys additional raw heparin from other Chinese suppliers. SPL says that the contamination occurred earlier in the supply chain.

Copyright © 2008 Associated Press

URL for this article:
http://online.wsj.com/article/SB120607644854754505.html

Copyright 2008 Dow Jones & Company, Inc. All Rights Reserved

This copy is for your personal, non-commercial use only. Distribution and use of this material are governed by our **Subscriber Agreement** and by copyright law. For non-personal use or to order multiple copies, please contact Dow Jones Reprints at 1-800-843-0008 or visit **www.djreprints.com**.

RELATED ARTICLES FROM ACROSS THE WEB

Related Articles from WSJ.com
- FDA Has Yet to Pinpoint Heparin Problem Feb. 29, 2008
- Beijing's Caveat Emptor Feb. 27, 2008
- China Confirms Itâ€™s the Source of Heparin Contaminant Mar. 20, 2008
- Heparin Likely Cut With Cheap Counterfeit Ingredient Mar. 19, 2008

Related Web News
- China's drug watchdog steps up controls on blood thinner heparin linked to ... Mar. 21, 2008 news.aol.com

More related content *Powered by Sphere*

THE WALL STREET JOURNAL.
ONLINE
March 26, 2008

Three More European Countries Recall Heparin

Denmark, France, Italy Raise Fresh Concerns About Chinese Supplies

By JEANNE WHALEN, THOMAS M. BURTON and ANNA WILDE MATHEWS
March 26, 2008; Page B4

Three European countries -- France, Italy and Denmark -- recalled the blood-thinning drug heparin or its ingredients, spreading recalls to new territories and raising the question of whether a previously trusted supplier may have contamination problems.

Associated Press
Shown here is an exterior view of pharmaceutical company Rotexmedica in northern Germany. Batches of heparin made at the plant have been recalled.

There is a potential worry for the U.S. in the new recalls of heparin, which is made from pig intestines. China's Shenzhen Hepalink Pharmaceutical Co., which supplies ingredients to **APP Pharmaceuticals** Inc. -- currently the sole supplier of large-dose heparin for surgery and kidney dialysis in the U.S. -- also supplied Italian company Opocrin SpA. On Tuesday, Opocrin said it bought some ingredients from Shenzhen that turned out to be contaminated.

APP, based in Schaumburg, Ill., said the Italian heparin ingredients were obtained through a different slaughterhouse than are APP's. APP heparin has consistently tested contaminant-free in its own and in U.S. Food and Drug Administration testing, APP spokeswoman Maili Bergman said Tuesday.

Shenzhen Hepalink couldn't be reached for comment.

Problems with tainted heparin first emerged in the U.S. in February, raising questions about the safety of the global supply chain for medicines and other products. **Baxter International** Inc. and a German company have recalled heparin products that were found to be contaminated. Both German authorities and Baxter have said the source of the contamination appears to be in China, where ingredients for the problematic heparin originated. The Chinese role has led to congressional investigations in the U.S., where lawmakers are calling for stepped-up scrutiny of

DOW JONES REPRINTS

R This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues, clients or customers, use the Order Reprints tool at the bottom of any article or visit: www.djreprints.com.

- See a sample reprint in PDF format.
- Order a reprint of this article now.

FURTHER READING

- FDA Identifies Contaminant in Heparin Batches[2] 03/20/08
- Heparin Faces Tougher Testing[3] 03/15/08
- Heparin Contaminant Is Found[4] 03/06/08
- China Says Drug Checks Are Up to Importers[5] 02/28/08
- Gaps Found in Chinese Drug Supply Chain[6] 02/21/08

foreign drug makers.

The FDA has said it now knows of 19 patients who have died after taking heparin, apparently from allergic reactions. It isn't clear how many of the patients who died had taken the Baxter product.

- **Latest Recalls:** Three European nations issued recalls for the blood-thinner heparin.
- **Precautionary Move:** Europe's drug regulator said it knew of no patients who suffered adverse reactions in the countries.
- **Contamination Fears:** The recalls reflect concern that the drug may contain the same contaminant found in U.S. batches of heparin.

The latest recalls in Europe showed the global problems with heparin spreading from Germany -- previously the only European country to recall heparin or its ingredients -- to three more countries.

There have been no reports of patients in France, Italy or Denmark suffering adverse events after taking heparin. But some batches of finished heparin and its active pharmaceutical ingredient are being recalled because they are contaminated or suspected of being contaminated, Martin Harvey-Allchurch, a spokesman for the European Union's drug regulator, the European Medicines Agency, based in London, said Tuesday.

"We presume it is the same contaminant," oversulfated chondroitin sulfate, as found in batches of heparin in the U.S., "but it has yet to be definitively confirmed," he said. The EMEA presumes this because the screening test being used is specifically designed to identify that particular contaminant, he said. The EMEA has been in close contact with the U.S. Food and Drug Administration on heparin and has passed along the FDA's contamination-screening test to all European Union countries, Mr. Harvey-Allchurch said. He added that he believed all EU countries are now testing their heparin batches for contamination.

In response to a question about the European recalls, Janet Woodcock, director of the U.S. Food and Drug Administration's drug center, said in a statement Tuesday that agency officials were "in communication with the regulatory authorities in these countries and are still vigorously pursuing our investigation."

An FDA spokeswoman said the agency has tested APP heparin batches in the past and found no contamination, and APP has promised to test the active ingredient for its U.S. heparin for the contaminant.

France on Friday started recalling finished heparin made by Rotexmedica GmbH, the same company that made heparin that was recalled from the German market earlier this month, Mr. Harvey-Allchurch said. Rotexmedica, a unit of France company Groupe Panpharma, couldn't be reached for comment.

Write to Anna Wilde Mathews at anna.mathews@wsj.com[1]

URL for this article:
http://online.wsj.com/article/SB120644563412062159.html

Hyperlinks in this Article:
(1) mailto:anna.mathews@wsj.com
(2) http://online.wsj.com/article/SB120593944533748617.html
(3) http://online.wsj.com/article/SB120551548809737105.html
(4) http://online.wsj.com/article/SB120473983548213973.html
(5) http://online.wsj.com/article/SB120411041290996553.html
(6) http://online.wsj.com/article/SB120354600035281041.html

Copyright 2008 Dow Jones & Company, Inc. All Rights Reserved

This copy is for your personal, non-commercial use only. Distribution and use of this material are governed by our **Subscriber Agreement** and by copyright law. For non-personal use or to order multiple copies, please contact Dow Jones Reprints at 1-800-843-0008 or visit **www.djreprints.com**.

RELATED ARTICLES FROM ACROSS THE WEB

Related Articles from WSJ.com

- FDA Raises Death Tally Related to Heparin Use Apr. 09, 2008
- U.S. to Step Up Testing Of Heparin Imports Mar. 14, 2008
- Germany Asks Companies Selling Heparin to Test for Contamination Mar. 12, 2008
- FDA Points Finger at China on Heparin Once More Apr. 21, 2008

Related Web News

- US regulators issue warning letter to Chinese firm over manufacturing of he... Apr. 22, 2008 news.aol.com
- China and U.S. Disagree Over Heparin Apr. 22, 2008 nytimes.com
- FDA sees possible fraud behind tainted heparin| Health Apr. 15, 2008 reuters.com
- What went wrong? Heparin probe highlights challenges of regulating global d... Apr. 11, 2008 news.aol.com

More related content *Powered by Sphere*

Outsourcing
-Pharma.com

Print

Breaking News on Outsourcing Pharma

Previous page : China watchdog responds to heparin scare; AZ now affected

China watchdog responds to heparin scare; AZ now affected

By Kirsty Barnes

30/03/2008- **China's drug regulatory authority is finally responding to curb its damaged reputation by urging its local authorities to take a more proactive role in stemming what is fast becoming a global heparin contamination, sparked by material sourced in the country.**

According to Chinese media reports, the State Food and Drug Administration (SFDA) issued a message on its website urging its regional offices to boost their supervision of the production methods of heparin manufacturers in their locality.

The watchdog has also urged heparin producers to source their raw heparin from registered suppliers only, and issued a plea to heparin manufacturers to ensure they are producing the material in accordance with the approved standards.

In addition, the SFDA warned manufacturers that they must take the initiative to closely follow the clinical effects of their products that are on the market and if any problems are linked back to their manufacturing facilities, they must halt production immediately and recall any implicated products from the market.

Moreover, the agency told raw heparin suppliers to tighten their management and quality checks of raw and supplementary materials.

The SFDA's latest actions indicate a softening of the stance on drug exports from the country that it took this time a month ago, when it effectively sent out a message to the world of "buyer beware".

The agency said last month that while it does enforce its own strict controls on the chemicals used in pharmaceuticals, "safeguarding the legality, quality and safety of active pharmaceutical ingredients (APIs)" is ultimately the responsibility of the importing country.

According to the SFDA, companies that manufacture APIs in China must be registered and certified as pharmaceutical companies by the watchdog after it carries out an inspection of the facility. It is this authority that importing firms and the regulatory agencies of importing countries should look for before accepting any product from a Chinese company.

In addition, any importing country should also still conduct their own stringent quality control tests on APIs, excipients and finished drugs, the agency said at the time.

While the watchdog's latest actions by no mean indicate it has changed its opinion on the matter of where the final responsibility for quality control lies, it does signal that it has recognised it still has a large role to play.

The agency's proactivity is overdue, considering the fact that China's already somewhat dubious pharma manufacturing reputation has been taking a beating for the past two months, at a time when the country's pharmaceutical industry has been actively trying to increase its international dealings.

What started as an isolated incident of contamination of certain lots of heparin sold by Baxter Healthcare in the US, of which the API was traced back to a supplier in China, has now spread to several countries across the globe, with multiple Chinese API suppliers also now implicated.

Hundreds of patients have reported severe adverse events and there are 19 deaths linked to the health scare.

It has since been revealed by a US Food and Drug Administration (FDA) investigation that the drug lots in question were contaminated with a substance called oversulfated chondroitin sulphate, which is made from animal cartilage and is a cheaper alternative to raw heparin, which is normally derived from pig's intestines. It is not approved for use in medicine.

So far, the US, Germany, France, Italy, Denmark, Switzerland and Japan have all pulled heparin products from the market due to the presence of contamination or as a precautionary measure after API links to China were made.

Australia and perhaps the UK are looking likely to be the next countries to follow suit. Australia's Therapeutic Goods Administration (TGA) recently issued a statement on its website claiming that it had discovered contamination in samples of heparin distributed by UK-based drug giant AstraZeneca.

Although there have been no increase in the number of adverse events reported from use of the drug, the regulator said that "it is unclear whether the contamination is related to single batches or affects heparin products more generally," as testing is still underway.

AstraZeneca has since confirmed that its heparin API was sourced form China and it is in discussions with the TGA to recall the affected product as soon as possible. The firm also indicated that it is now evaluating its China supply chain.

Copyright - Unless otherwise stated all contents of this web site are © 2000/2008 – Decision News Media SAS – All Rights Reserved. For permission to reproduce any contents of this web site, please email our Syndication department: contact our Syndication department. Full details for the use of materials on this site can be found in the Terms & Conditions.

contact the editor

Print

16 of 31 DOCUMENTS

The New York Times

March 30, 2008 Sunday
Late Edition - Final

The Drug Scare That Exposed a World of Hurt

BYLINE: By WALT BOGDANICH

SECTION: Section WK; Column 0; Week in Review Desk; THE WORLD; Pg. 3

LENGTH: 1052 words

When cold medicine containing a poison made in China killed nearly 120 Panamanians in 2006 and early 2007, Americans could take some comfort in the belief that a similar epidemic could never happen here, not with one of the best drug regulatory systems in the world.

Then last spring, hundreds if not thousands of pets died or were sickened in the United States by a Chinese pet food ingredient that contained lethal levels of melamine, an industrial product used to artificially boost protein levels. That was followed quickly by the discovery that Americans were brushing their teeth with Chinese toothpaste containing a poisonous chemical used in antifreeze.

Still, no Americans died from the chemical.

And then came heparin.

A hugely popular blood thinner used in surgery and dialysis, heparin turned out in some cases to contain a mystery substance that sophisticated lab tests earlier this month determined to be a chemically modified substance that mimics the real drug. The United States **Food and Drug Administration** has linked it to 19 deaths and hundreds of severe allergic reactions, though the agency is still investigating whether the contaminant was the actual cause.

What a difference a year makes.

After many near misses and warning signs, the heparin scare has eliminated any doubt that, here and abroad, regulatory agencies overseeing the safety of medicine are overwhelmed in a global economy where supply chains are long and opaque, and often involve many manufacturers.

"In the 1990s governments were all about trying to maximize the volume of international trade," said Moises Naim, editor in chief of Foreign Policy magazine and author of "Illicit: How Smugglers, Traffickers and Copycats Are Hijacking the Global Economy." "I'm all for that, but I believe this decade is going to be about maximizing the quality of that trade, not quantity."

Mr. Naim said the heparin scare is already having a "huge" impact, fueling worldwide anxiety over imported medicine and a growing demand for consumer protection.

Congressional Democrats are talking about authorizing more money so the **F.D.A.** can do more overseas inspections, particularly in China, where more and more drug ingredients are made. The agency is also completing a plan to permanently station employees in China for the first time.

"Just focusing on the borders of the United States does not work," said Dr. Murray Lumpkin, a deputy commissioner at the **F.D.A.** "In order for us to do our job better domestically, we have to work better internationally."

Chinese drug regulators have also begun to take small steps toward plugging some of the country's gaping regulatory holes, particularly with the thousands of chemical companies that sell pharmaceutical ingredients without a drug license.

Regulators have much to do and many obstacles to overcome in trying to adapt to changes brought on by globalization.

The way heparin is made and distributed illustrates the challenges they face. The drug's raw material comes from mucous membranes in the intestines of slaughtered pigs. Those membranes are mixed together and cooked, a process that in China often takes place in unregulated family workshops.

It is then transported to middlemen, called consolidators, who direct the product to plants in China that manufacture heparin's active ingredient for shipment to either another trader or the finished dose manufacturer. In the United States, the tainted ingredients ended up at Baxter International, which later had to recall the blood thinner.

Since the outbreak in the United States, Japan and several countries in Europe have recalled certain heparin products made with Chinese ingredients. In some instances, European traders buy and sell the heparin to companies in other countries, extending the supply chain even more.

Anti-counterfeiting experts say that the longer the chain, the greater the opportunity for counterfeiters to adulterate the product. In fact, **F.D.A.** investigators have yet to figure out where in the multistage manufacturing process the chemical that mimics heparin was added.

"Advanced technology and global manufacturing outlets have made fake drugs a big and illicit business that is literally poisoning patients," said Alan C. Drewsen, executive director of the International Trademark Association.

And since supply chains often pass through more than one country, there is no government agency with the power to police all of it. The World Health Organization runs a program that helps track counterfeit medicine, but it has no regulatory authority.

Manufacturers also need to do a better job of testing imported ingredients, drug experts say.

For example, tests failed to detect the heparin-like contaminant because it was so similar to the real thing. And that worries Dr. Roger L. Williams, chief executive of the United States Pharmacopeia, which sets quality standards for medicine and supplements.

"What you are seeing here is the tip of the iceberg," Dr. Williams said. "How do we know what else has gone wrong?"

He said, for example, that melamine was missed because "we have a bad test for protein." Other tests should also be improved, he said. To help companies identify diethylene glycol, the inexpensive poison that ended up in Panamanian cold medicine and in Chinese toothpaste, USP recently came up with a better way of determining if that poison is present.

Some leading members of Congress don't want to rely so heavily on manufacturers to protect the public, particularly afterreports said poor management and scientific inadequacies have weakened the **F.D.A.**

More than 500 plants in China export drug ingredients to the United States but the agency inspected only 13 of them last year.

One of the plants not inspected was the one that made the contaminated heparin ingredient. That plant, Changzhou SPL, blames someone else further upstream in the supply chain for selling tainted raw materials.

The **F.D.A.** is continuing to investigate.

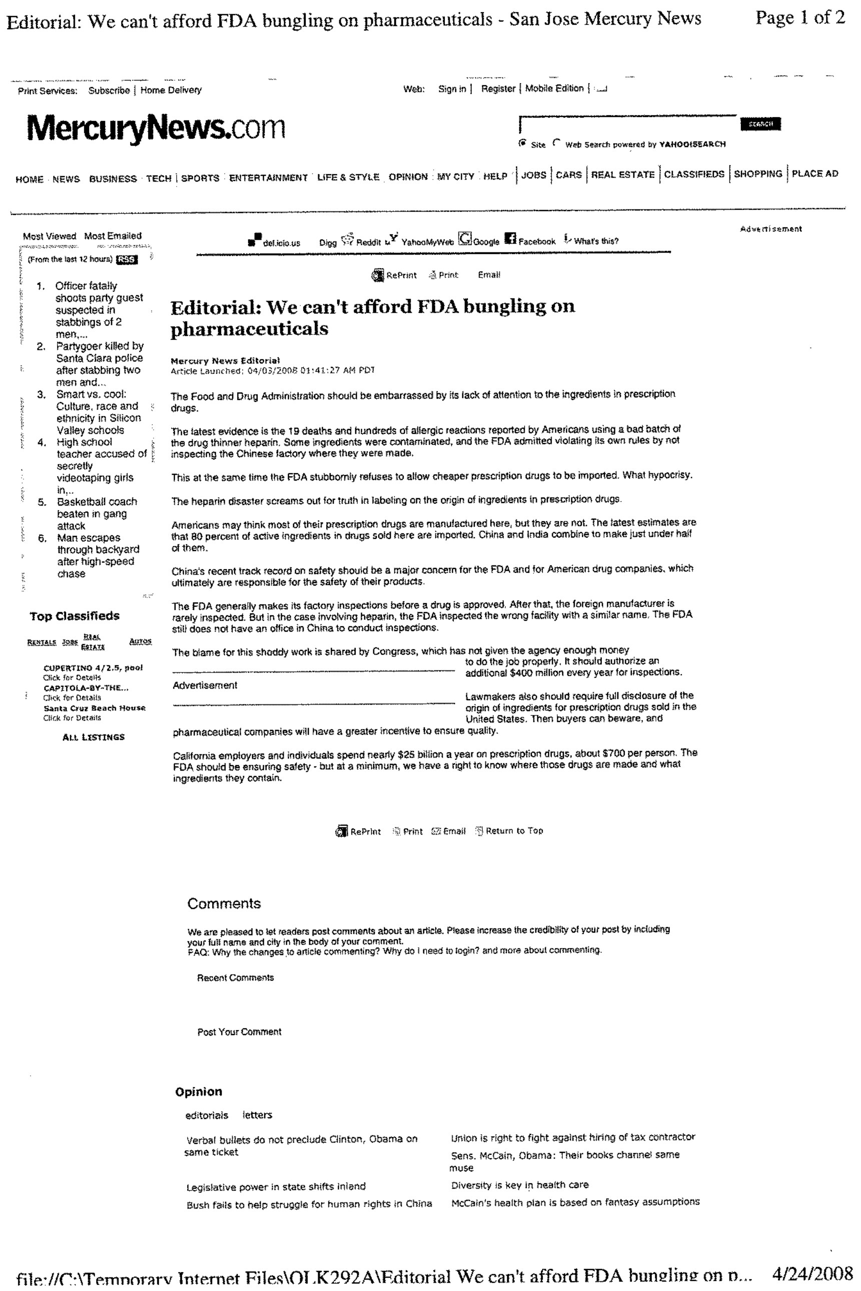
"We can blame the Chinese for this stuff as much as we want, but the truth of the matter is we are the people who are buying," said Joseph G. Acker, president of a chemical trade association.

And Mr. Acker points a finger at the **F.D.A.**, adding, "I think that organization needs a total overhaul."

URL: http://www.nytimes.com

LOAD-DATE: March 30, 2008

LANGUAGE: ENGLISH



Editorial: We can't afford FDA bungling on pharmaceuticals - San Jose Mercury News Page 1 of 2

Print Services: Subscribe | Home Delivery
Web: Sign in | Register | Mobile Edition |
MercuryNews.com
SEARCH
● Site ○ Web Search powered by YAHOO!SEARCH
HOME NEWS BUSINESS TECH | SPORTS ENTERTAINMENT LIFE & STYLE OPINION MY CITY HELP | JOBS | CARS | REAL ESTATE | CLASSIFIEDS | SHOPPING | PLACE AD
Most Viewed Most Emailed
(From the last 12 hours) RSS

1. Officer fatally shoots party guest suspected in stabbings of 2 men,...
2. Partygoer killed by Santa Clara police after stabbing two men and...
3. Smart vs. cool: Culture, race and ethnicity in Silicon Valley schools
4. High school teacher accused of secretly videotaping girls in,..
5. Basketball coach beaten in gang attack
6. Man escapes through backyard after high-speed chase

Top Classifieds

CUPERTINO 4/2.5, pool
Click for Details
CAPITOLA-BY-THE...
Click for Details
Santa Cruz Beach House
Click for Details

ALL LISTINGS

del.icio.us Digg Reddit YahooMyWeb Google Facebook What's this?
RePrint Print Email
Advertisement

Editorial: We can't afford FDA bungling on pharmaceuticals

Mercury News Editorial
Article Launched: 04/03/2008 01:41:27 AM PDT

The Food and Drug Administration should be embarrassed by its lack of attention to the ingredients in prescription drugs.

The latest evidence is the 19 deaths and hundreds of allergic reactions reported by Americans using a bad batch of the drug thinner heparin. Some ingredients were contaminated, and the FDA admitted violating its own rules by not inspecting the Chinese factory where they were made.

This at the same time the FDA stubbornly refuses to allow cheaper prescription drugs to be imported. What hypocrisy.

The heparin disaster screams out for truth in labeling on the origin of ingredients in prescription drugs.

Americans may think most of their prescription drugs are manufactured here, but they are not. The latest estimates are that 80 percent of active ingredients in drugs sold here are imported. China and India combine to make just under half of them.

China's recent track record on safety should be a major concern for the FDA and for American drug companies, which ultimately are responsible for the safety of their products.

The FDA generally makes its factory inspections before a drug is approved. After that, the foreign manufacturer is rarely inspected. But in the case involving heparin, the FDA inspected the wrong facility with a similar name. The FDA still does not have an office in China to conduct inspections.

The blame for this shoddy work is shared by Congress, which has not given the agency enough money to do the job properly. It should authorize an additional $400 million every year for inspections.

Advertisement

Lawmakers also should require full disclosure of the origin of ingredients for prescription drugs sold in the United States. Then buyers can beware, and pharmaceutical companies will have a greater incentive to ensure quality.

California employers and individuals spend nearly $25 billion a year on prescription drugs, about $700 per person. The FDA should be ensuring safety - but at a minimum, we have a right to know where those drugs are made and what ingredients they contain.

Comments

We are pleased to let readers post comments about an article. Please increase the credibility of your post by including your full name and city in the body of your comment.
FAQ: Why the changes to article commenting? Why do I need to login? and more about commenting.

Recent Comments

Post Your Comment

Opinion

Verbal bullets do not preclude Clinton, Obama on same ticket
Legislative power in state shifts inland
Bush fails to help struggle for human rights in China
Union is right to fight against hiring of tax contractor
Sens. McCain, Obama: Their books channel same muse
Diversity is key in health care
McCain's health plan is based on fantasy assumptions

file://C:\Temporary Internet Files\OLK292A\Editorial We can't afford FDA bungling on p... 4/24/2008

washingtonpost.com

Rise in Price Was a Sign of Trouble

Advertisement

Supply Problems Caused Spike That Some Say Should Have Prompted Scrutiny

By Marc Kaufman
Washington Post Staff Writer
Sunday, April 13, 2008; A03

The price of the Chinese-produced main ingredient used to make the blood thinner heparin doubled last year, just four months before hundreds of American patients began having severe and sometimes fatal allergic reactions to the medication, according to a report from an authoritative drug information company in China.

The highly unusual increase of the price within a quarter of a year should have been a red flag to drugmakers that something significant -- and perhaps dangerous -- was happening to the ingredient of a medication widely used in life-threatening situations, industry experts said. Heparin contains a substance that is extracted from the intestines of pigs and is collected in slaughterhouses and on farms.

Between November and February, hundreds of Americans experienced serious allergic reactions after taking Chinese-made heparin, and 62 died, the Food and Drug Administration reported this week, sharply increasing its previous estimates. Some patients always respond poorly to heparin, but FDA statistics show three fatal allergic reactions in 2006.

Last month, the agency discovered through chemical testing that heparin made in China and distributed in the United States by Baxter International had been contaminated with inexpensive over-sulfated chondroitin, an altered version of a widely used dietary supplement.

The company that bought the Chinese raw material and began processing the drug -- Scientific Protein Laboratories (SPL) of Waunakee, Wis., and Changzhou, China -- acknowledged this week that the price of unprocessed heparin doubled in China in the last half of 2007 and said the company passed on some of the increase to its customers. Baxter spokeswoman Erin Gardiner said that the company faced "modest" price increases in 2007 because it had long-term contracts, but that it saw a "substantial" rise this year.

Wayne Pines, an SPL spokesman, attributed the price spike to a supply shortage caused by an epidemic of "blue ear" disease in Chinese pigs and by decisions of Chinese villages and companies to get out of pig farming and shift to more lucrative businesses. Pines said the price doubling did not raise any safety concerns.

But some businesspeople who deal in pharmaceuticals said the sudden increase in the long-stable price of an important ingredient should have raised concern among purchasing agents.

"This price increase should be, has to be, seen as a signal to purchasing managers," said Guy Villax, chief executive of the European drug company Hovione and a board member of the European trade association for drug ingredient makers.

"You have a situation here where the supply chain begins in slaughterhouses and villagers' homes, and a sudden disruption of that supply doesn't raise safety questions? I don't know whether anyone could have detected the contaminant early on, but at least they should have been looking," he said.

Villax added that the supply shortage and the steep price increase offered an obvious opportunity for individuals "who don't play by the rules" to make windfall profits by adding cheaper materials to the raw heparin as a way to meet the demand.

The FDA has not said whether it thinks the contaminant was intentionally added to the drug, but officials described it as a heparin-like compound that appeared to have been formulated so that standard quality-control tests could not detect it.

Although officials have not conclusively linked the contaminant to the allergic reactions and deaths, they have said there is clearly an overlap between the two. Chondroitin sulfate does not occur naturally but can be made from pig cartilage.

FDA spokeswoman Karen Riley said Friday that the agency was aware that the price of raw heparin increased dramatically last year but did not necessarily see it as a signal of potential quality problems. The rise was apparently the result of the blue ear disease outbreak, she said, but the agency is looking at other possibilities.

"We are aware that with other products in other years, ingredients that look like the approved drug have been added for economic advantage, to make a quick buck," she said.

The price increase is detailed in a report by the Chinese drug information company Oriental Health E-Commerce Business (Beijing), recently renamed Healthoo.com. The company collects data on drug sales and prices from Chinese customs offices and is considered authoritative by Western businesspeople. The heparin report, made public only recently, contains statistics but no commentary.

The Healthoo report shows that the price of crude heparin exported from China went from $629 per kilogram in January 2007 to $1,507 per kilogram in December. The report also shows that more than 50 percent of the crude heparin went to the United States, 37 percent to Germany and the rest to other nations.

The report shows that the cost of refined heparin exported by China rose at about the same rate as that of raw heparin -- strongly suggesting that the increase was driven by the price of the raw material, rather than by processing problems.

In recent years, China has been the world's primary source for the active ingredient in heparin, but in an e-mail Friday, Healthoo said that significantly less heparin is being exported from China now because of the supply problems.

No heparin deaths have been documented in other countries, but the contamination was detected and allergic reactions were reported in France, Germany, Italy and elsewhere. It is unclear whether the lack of reported deaths outside the United States is because of differences in the sources of heparin or of a more aggressive U.S. system of reporting adverse events.

Heparin, which is used as a blood thinner during surgery and dialysis, has been on the market since the 1930s. Like many pharmaceuticals -- especially inexpensive generic drugs -- it is now largely made abroad, increasingly in lightly regulated nations such as China and India. The FDA's ability to oversee the supply chains has become a much-discussed issue on Capitol Hill.

Brant Zell is past chairman of the Bulk Pharmaceuticals Task Force, a group within a larger American organic-chemicals trade association that deals with drug ingredients. He said unusual price spikes, such as the one involving heparin, have buyers "asking questions like, 'Is something unethical going on here?' "

He said the case highlights a new reality -- that when a problem arises with an American-manufactured drug, the FDA usually addresses it quickly and can take action promptly. But when a problem surfaces in China or India, where regulation and oversight are far less strict, it inevitably takes officials longer to determine what is happening and why.

"The truth is that there's not a level playing field here when it comes to regulation in the United States versus a place like China," Zell said. "And since many Chinese are quite a few years behind us in understanding quality control and good manufacturing, problems like with heparin will be hard to avoid because it's just harder to pick up the early warning signals."

Jon Martino, a specialist in tracking and detecting counterfeit drugs and a former global investigations manager for Amgen, a major biotech company, said that U.S. firms that get their unprocessed heparin from China are to some extent "at the mercy" of their suppliers.

"Baxter is dependent on getting" that active pharmaceutical ingredient and "would drop to their knees to get it for their patients," he said. "Maybe they thought it was a temporary glitch in price, maybe they didn't do their due diligence as well as they could have. But the basic point is that they need to get those ingredients, because they have so many customers to supply."

Staff writer Mary Pat Flaherty contributed to this report.

View all comments that have been posted about this article.

Post a Comment

View all comments that have been posted about this article.

You must be logged in to leave a comment. Login | Register

Submit

Comments that include profanity or personal attacks or other inappropriate comments or material will be removed from the site. Additionally, entries that are unsigned or contain "signatures" by someone other than the actual author will be removed. Finally, we will take steps to block users who violate any of our posting standards, terms of use or privacy policies or any other policies governing this site. Please review the full rules governing commentaries and discussions. You are fully responsible for the content that you post.

© 2008 The Washington Post Company

Ads by Google

10 Rules to Cut Belly Fat
Lose 9 lbs every 11 Days with these 10 Idiot Proof Rules of Fat Loss.

4-13-08

THE CANADIAN PRESS

Go to Google News

Heparin probe highlights challenges of regulating global drugs market

1 day ago

CHANGZHOU, China — On a dusty lane in east China, a small factory sitting amid strawberry and vegetable fields processes chemicals from pig guts into heparin, a commonly used blood thinner linked to 62 deaths and hundreds of allergic reactions in the U.S. and Germany.

The mysterious problems with heparin from the factory and others like it - China's deadliest product quality scandal since Chinese cough syrup killed 93 people in Central America a year ago - dramatically illustrate the perils of shifting drug production offshore.

With recalls of heparin products now in six countries, it is an issue that regulators are scrambling to address. Some specific heparin products and certain lots from B. Braun Medical Inc. that were distributed in Canada are among those recalled in recent weeks.

In the past month, China's drug safety agency has ordered tighter controls on heparin production. That followed a U.S. Food and Drug Administration order requiring all heparin imports to be tested. The FDA also announced plans to station eight regulators in China and hire five Chinese to work with them.

"This is just the tip of the iceberg in terms of problems with sensitive drugs," said Dr. Bryan Liang, an adviser to the Partnership for Safe Medicines, an American group working to promote drug safety. "The problem is only going to get worse as more materials come from suspect sources."

About 40 per cent of pharmaceuticals and 80 per cent of the chemical ingredients in drugs are imported, according to U.S. government statistics. A growing share comes from developing countries such as China, India and Mexico that are still building their own drug safety systems.

Heparin is derived from mucous wrung and washed from pig intestines and other animal organs. It has been used for decades to prevent clotting from intravenous procedures, dialysis and heart surgery.

The recent problems were traced to heparin made in China and marketed in the United States; so far, China has reported no allergic reactions to heparin used locally.

The U.S. FDA announced Tuesday that it had found 62 deaths and nearly 800 severe allergic reactions associated with heparin.

Health Canada's adverse drug reaction monitoring database does not show an increase in reports related to heparin in 2007. One report of an allergic adverse reaction was reported to the monitoring program last year.

"From January 1, 2008 to April 4, 2008, Health Canada has received a total of 14 adverse reaction reports suspected to be associated with heparin," a Health Canada spokesman said Thursday in an email.

"Two of the 14 reports described allergic type reactions. These two reports of allergic type reactions did not have a fatal outcome. In these two reports of allergic type reactions, neither the specific brand nor the lot of heparin was provided."

A caveat on the database stresses that these reports should not be used to determine the incidence of a reaction or for estimating risk of a particular product, as the total number of reactions occurring and the number of patients exposed to the product aren't known.

In the U.S., the first reports of deaths were linked to products sold by Deerfield, Ill.-based Baxter International Inc., the biggest heparin seller in the U.S. But the most recent figures also included patients treated with other brands of heparin.

Baxter recalled nearly all its U.S. heparin injections, as have several other companies.

German manufacturer RotexMedica GmbH recalled batches of heparin from China after some 80 reports of allergic reactions, but no deaths.

Danish, French and Italian authorities also recalled batches of potentially contaminated heparin from China as a precaution, the European Medicines Agency said last month.

Three Japanese drug companies and a U.S. manufacturer, B. Braun Medical Inc., also recalled heparin products from Baxter's supplier, Waukanee, Wis.-based Scientific Protein Laboratories, which owns the factory sitting among farm fields outside of Changzhou, a sprawling industrial city west of Shanghai.

The FDA says a contaminant, identified as oversulphated chondroitin sulphate, accounted for up to half of the active ingredient in some batches of heparin from the factory, known as Changzhou SPL. It has yet to confirm, though, whether the contaminant caused the allergic reactions.

Chondroitin sulphate, usually made of animal or shark cartilage, is used as a food supplement for joint pain. It is more than seven times cheaper than heparin, which might tempt suppliers somewhere along the production chain to substitute it. And its chemical similarity to heparin makes it hard to spot, the FDA said.

Heparin was first made in North America and Europe, but production has shifted to lower-cost developing countries over the past 20 years. The raw chemicals, or active pharmaceutical ingredients, used to make it and many other drugs are now mostly imported from China and India.

"We have an increasingly globalized supply chain," said James Shen, publisher of the industry newsletter Pharma China. "The Chinese are now major suppliers of bulk pharmaceuticals and also supply intermediate chemicals for drugs."

"It is likely we will continue to see the same problems with other drugs," he added.

The U.S. FDA inspects only about seven per cent of foreign drug makers each year; it failed to inspect Changzhou SPL because of what it says was a language mistake.

The raw chemicals for the drug are usually made in small, unregulated workshops, using pig guts from slaughterhouses and sausage-casing factories, processed by chemical companies and eventually drug makers before being delivered to hospitals.

"The supply chain that was used to make the materials is impossible to follow," said Liang of the Partnership for Safe Medicines in Virginia. "Add to that, Chinese manufacturers are not averse to cutting corners, as we've seen in toys, toothpaste, food and drugs."

When FDA experts belatedly inspected Changzhou SPL last month, they found scratched tanks with "unidentified material" sticking to their insides. Records were missing for some of its sources of raw heparin, and testing was incomplete.

"We are a company with high standards. We have nothing more to say to you!" shouted a manager at Changzhou SPL who answered the phone but refused to give his name.

"We have never had chondroitin sulphate on our production list. Just see the official announcements," he said before slamming the phone down.

A Scientific Protein Laboratories statement emphasized that FDA findings suggest the chondroitin sulphate was in the affected heparin before it reached Changzhou SPL.

"The observations made by the FDA during its inspection do not indicate any fundamental or underlying problems with the Changzhou SPL facility," the statement said, quoting industry consultant Robert Rhoades speaking on SPL's behalf.

Importers beware is the principle governing all international trade in drugs and pharmaceutical chemicals, said Shen of Pharma China.

"For exports, (China) doesn't regulate anything at all. There is no export licensing system in place," he said, noting that such chemicals are generally unregulated. "The U.S. FDA doesn't regulate those exports from the U.S. either."

FDA officials say a U.S.-China agreement on improving co-operation in drug safety, signed in December, has helped the heparin investigation, though heparin was not on the original list of drugs covered by the pact.

Even with inspections, heparin is tricky, said Liu Jian, an expert on the chemical at the University of North Carolina.

"In producing heparin, it's very important to control the quality of the raw heparin," Liu said. "Once you have a contaminant that you didn't get rid of in the early stages, it's very hard to tell what you have there."

On the Net:

- U.S. Food and Drug Administration: http://www.fda.gov
- China State Food and Drug Administration: http://www.sfda.gov.cn
- Health Canada: http://www.hc-sc.gc.ca

Hosted by Google

washingtonpost.com

U.S. and China Dispute Conclusions About Tainted Heparin

Advertisement

By Marc Kaufman
Washington Post Staff Writer
Monday, April 21, 2008; 4:11 PM

American and Chinese officials publicly disputed each other's conclusions today about what caused a deadly spike in severe reactions to the blood thinning drug heparin. Each side essentially said that the other was to blame.

Chinese officials today rejected the Food and Drug Administration's conclusion that a synthetic compound from China found in tainted supplies of the blood thinner heparin was the likely cause of the hundreds of injuries and deaths associated with the drug. Later, Janet Woodcock, director of the agency's Center for Drug Evaluation and Research, said that extensive research had convinced the agency that tainted heparin from China had indeed caused the reactions.

In addition, Woodcock said that the contaminated heparin had been found in 11 nations, and that at least 12 Chinese companies had some batches of the tainted drug ingredient.

In the Chinese government's first public statements on the controversy, Jin Shaohong, a top official with the Chinese National Institute for the Control of Pharmaceutical and Biological Products, said the compound -- oversulfated chondroitin -- could not be "the root cause" of the adverse reactions to heparin, as the FDA has suggested.

Speaking at the Chinese Embassy in Washington, Jin said some of the batches of heparin associated with severe allergic reactions and distributed by Baxter International did not have the synthetic chondroitin in them. He also said heparin with the contaminant has been found in more than 10 other nations, but none has reported a similar spike in harmful allergic reactions.

Jin said the Chinese government was conducting its own investigation of the heparin issue that would include a visit tomorrow to Baxter's New Jersey manufacturing plant. He said the allergic reactions could have been created by impurities introduced while the raw heparin from China was further refined by Scientific Protein Laboratories (SPL) of Wisconsin and then prepared for distribution in New Jersey.

Jin said he wanted to visit the Baxter plant and take back some samples of the company's heparin for "further in-depth analysis and investigation," because "when you see it, you believe it."

Baxter spokeswoman Erin Gardiner said that her company disagreed with the Chinese conclusions, and that the oversulfated chondroitin appeared to be the problem. She also said the Chinese were incorrect when they said some batches of heparin that caused severe reactions did not contain the chondroitin.

Representatives of more than 12 nations, including the Chinese, joined the FDA last week in a closed-door meeting on heparin. This morning, the FDA issued a warning letter to the Chinese supplier of heparin, Changzhou SPL Company Ltd., which is wholly owned by SPL.

"Equipment used to manufacture heparin sodium USP is unsuitable for its intended use," the FDA told the supplier. Agency inspectors, who visited the Chinese facility in late February, also found that the company did not properly evaluate its own suppliers, who provide crude ingredients from pig intestines.

The Chinese plant has been supplying heparin for American patients since 2004. The FDA acknowledged last month that it never inspected the plant because it confused it with another facility with a similar name, and Chinese officials said they did not inspect it because it was listed as a plant producing chemicals rather than pharmaceuticals.

The sharp spike in allergic reactions to heparin from November through February has become emblematic of the large and growing number of prescription drugs and drug ingredients being imported from lightly-regulated nations such as China and India. It has also highlighted the question of whether the FDA has the resources and will to regulate foreign-made drugs with the same intensity that it does American-made products. Numerous members of Congress have called for greater oversight, and the FDA has announced that it will soon open its first office in China.

The complexity of the issue was apparent at the Chinese Embassy news conference. Jin said categorically "that the results of our recent investigation and other available evidence do not support the theory that the root cause" of adverse reactions to heparin has been the oversulfated chondroitin that the FDA identified as the likely culprit. He said Chinese officials are as eager to find what caused the problems as Americans.

Post a Comment

View all comments that have been posted about this article.

You must be logged in to leave a comment. Login | Register

Submit

Comments that include profanity or personal attacks or other inappropriate comments or material will be removed from the site. Additionally, entries that are unsigned or contain "signatures" by someone other than the actual author will be removed. Finally, we will take steps to block users who violate any of our posting standards, terms of use or privacy policies or any other policies governing this site. Please review the full rules governing commentaries and discussions. You are fully responsible for the content that you post.

© 2008 The Washington Post Company

Ads by Google

www.chicagotribune.com/business/chi-heparin-china-factory-fda-apr21,0,5583524.story

chicagotribune.com

FDA: Heparin supplier's Chinese factory 'unsuitable'

By Bruce Japsen

Tribune staff reporter

2:41 PM CDT, April 21, 2008

The U.S. Food and Drug Administration today said a Wisconsin company's Chinese plant used to make the blood thinner heparin's active ingredient was "unsuitable for its intended use" and was not in a position to detect impurities in the product now linked to hundreds of potentially deadly allergic reactions.

The FDA is probing the China-based supply chain, where the active ingredient in heparin made by Baxter International Inc. originates. Health officials suspect it may have been intentionally contaminated with an animal-like substance similar to heparin that was put into the product to increase certain suppliers' profits.

In a stern warning letter to the general manager of Scientific Protein Laboratories (SPL's) Changzhou China plant manager that was released today, the FDA said its inspection two months ago of the plant revealed "significant deviations" from U.S. good manufacturing practices. In addition, the FDA said the plant's processing steps used to manufacturing heparin's active ingredient provided "no assurance" any impurities could have been effectively removed.

The plant was inspected in February for the first time despite several years of manufacturing heparin's active ingredient. FDA officials said the plant's inspection did not occur earlier because of a paperwork glitch.

For its part, Scientific Protein said the warning letter does not reflect Changzhou SPL's "actual state of compliance." Neither the FDA nor SPL or Baxter has revealed an exact root cause of the allergic reactions.

But SPL said the contaminant was introduced earlier in a supply chain that stretches through farm villages to hog farms in rural China.

"The contaminant found in certain lots of finished heparin product was not introduced in the manufacturing processes at Changzhou SPL or SPL," Scientific Protein said in a statement. "Based upon testing of crude heparin materials and reports from other manufacturers around the world, it is now clear that the suspect contaminant was introduced earlier in the supply chain in China and was widespread throughout the unrelated Chinese supply chains of many companies."

The FDA has said there are now 62 reports of deaths of patients who experienced one or more allergic reactions and who were infused with heparin from Jan. 1, 2007, through the end of last month, the agency said.

Baxter, meanwhile, is standing by its estimate of four deaths associated with its heparin since the beginning of last year.

bjapsen@tribune.com

Copyright © 2008, Chicago Tribune

The New York Times

ROCK 'N ROLL WILL NEVER DIE

April 22, 2008

U.S. Identifies Tainted Heparin in 11 Countries

By GARDINER HARRIS

WASHINGTON — A contaminated blood thinner from China has been found in drug supplies in 11 countries, and federal officials said Monday they had discovered a clear link between the contaminant and severe reactions now associated with 81 deaths in the United States.

But a Chinese official disputed the assertion that the contaminant found in the drug, heparin, caused any deaths and insisted that his country's inspectors be allowed to inspect the American plant where the finished heparin vials were made. He said any future agreement to allow American inspections of Chinese firms should be reciprocal.

"We don't have a strong evidence to show that it is heparin or its contaminant that caused the problem," said the official, Ning Chen, second secretary at the Chinese Embassy.

Mr. Chen said that illnesses associated with contaminated heparin had occurred only in the United States, which he said suggested that the problem arose in this country.

Dr. Janet Woodcock, director of the Food and Drug Administration's drug center, said that German regulators uncovered a cluster of illnesses among dialysis patients who took contaminated heparin. She said Chinese officials had conceded that heparin produced in their country contained a contaminant, though they say it was not connected to the illnesses.

"Heparin should not be contaminated, regardless of whether or not that contamination caused acute adverse events," Dr. Woodcock said. "We are fairly confident based on the biological information that we have had that this contaminant is capable of triggering these adverse reactions."

The dispute is a sign of growing tensions between China and the United States over the safety of Chinese imports. China has in recent years exported poisonous toothpaste, lead-painted toys, toxic pet food, tainted fish and now, contaminated medicine.

Bills to require far more aggressive inspections of Chinese products and companies are being proposed by members of Congress. Hearings are scheduled for Tuesday in the House and Thursday in the Senate.

China has lurched between defensiveness and cooperation on issues of product safety. Last year, it initially blocked the F.D.A. from investigating tainted pet food and accused foreign forces of exaggerating the issue. Then in July, China said that it had executed its former top food and drug regulator for taking bribes and promised reforms.

The F.D.A. sent a warning letter on Monday to Changzhou SPL, the Chinese plant identified as the source of contaminated heparin made by Baxter International in the United States. It warned that the plant used unclean tanks to make heparin, that it accepted raw materials from an unacceptable vendor and that it had no adequate way to remove impurities.

Heparin is made from the mucous membranes of the intestines of slaughtered pigs that, in China, are often cooked in unregulated family workshops. The contaminant, identified as oversulfated chondroitin sulfate, a cheaper substance, slipped through the usual testing and was recognized only after more sophisticated tests were used.

The F.D.A. has identified 12 Chinese companies that have supplied contaminated heparin to 11 countries — Australia, Canada, China, Denmark, France, Germany, Italy, Japan, the Netherlands, New Zealand and the United States. Deborah Autor, director of compliance at the F.D.A.'s drug center, said the agency did not know the original source of all the contamination or the points in the supply chain at which it was added.

Officials have discovered heparin lots that included the cheap fake additive manufactured as early as early as 2006, although a spike in illnesses associated with contaminated heparin began in November and persisted through February, officials said.

Separately, the Government Accountability Office will release a report on Tuesday showing that the F.D.A. would need to spend at least $56 million more next year to begin full inspections of foreign plants. It would need to spend at least $15 million annually to inspect China's drug plants every two years, which is the domestic standard.

Bush administration officials have acknowledged problems associated with poor inspection of overseas plants and have plans to improve the situation. But President Bush's budget does not provide the F.D.A. with funds to hire more inspectors.

At its present inspection pace, the F.D.A. would need at least 27 years to inspect every foreign medical device plant that exports to the United States, 13 years to check every foreign drug plant and 1,900 years to examine every foreign food plant.

Proposals circulating on Capitol Hill would increase the agency's financing and charge domestic and foreign manufacturers fees to pay for inspections.

"Even the Bush administration seems to understand the potential peril that these foreign firms pose, but they offer only vague plans to address the problems and they refuse to spend more than a fraction of the money needed to protect the public," said Representative John D. Dingell, a Michigan Democrat who leads the House Committee on Energy and Commerce.

The F.D.A. has announced plans to open inspection offices in three Chinese cities, but the agency has yet to get permission from the Chinese government. Mr. Chen said any inspection agreement should be reciprocal. "Will the U.S. government accept the Chinese F.D.A. to set up in the United States?" he said.

Dr. Woodcock said the Chinese had agreed to test heparin lots before allowing them to be exported. But Dr. Moheb Nasr, director of the drug agency's office of new drug quality assessment, said that the Chinese test might not be sensitive enough to identify the contaminant.

Dr. Woodcock assured patients, however, that all heparin supplies in the United States had been tested with the most sensitive assays and had been found to be uncontaminated.

Scientific Protein Laboratories and Changzhou SPL said the company regretted the agency's decision to send a warning letter that, it said, did not reflect the company's current safety practices. The company said it had no way of detecting a contaminant present in heparin supplies throughout China.

Baxter International, which bought heparin ingredients from SPL and sold the finished drug in the United States, said that its tests confirmed that the contaminant could cause illness. It disputed the F.D.A.'s analysis that its product was linked with 81 deaths, saying it had identified only 5 in which its product "may have contributed to the adverse outcome, though there is not yet enough medical data available to draw a firm conclusion that the reaction caused the death."

Deaths linked to the drug may have been concentrated in the United States because American doctors may be more likely to use large, quickly infused amounts of the drug, said drug officials. Also, the F.D.A. may track serious side effects better than its counterparts abroad.

Copyright 2008 The New York Times Company

THE WALL STREET JOURNAL.
ONLINE

April 22, 2008

U.S., China Clash Over Heparin

Tainted Supplies Called Global Issue; Beijing Rebuts FDA

By **ALICIA MUNDY and THOMAS M. BURTON**
April 22, 2008

WASHINGTON -- U.S. and Chinese officials clashed Monday over where to lay blame for contamination of supplies of heparin, a widely used blood thinner.

The U.S. Food and Drug Administration called the contamination "a world-wide problem" that has appeared in 11 countries including the U.S. and is linked to as many as 81 deaths.

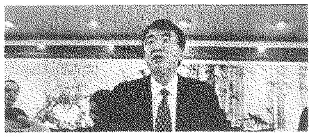
- **The News:** The FDA and China clashed over problems with the blood thinner heparin.
- **The Arguments:** The FDA said contaminated heparin affects at least 11 countries and is linked to 81 deaths since last year. China disputes the contention that the problem involves China-based firms.
- **What's Next:** A proposed bill strictly regulating food and drug imports will get a push at a congressional hearing Tuesday.

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said heparin contaminated with over-sulfated chondroitin sulfate has been traced to 12 companies in China.

Hours before Dr. Woodcock spoke, the Chinese government began a pushback against the FDA's conclusions that over-sulfated chondroitin is linked to bad reactions and that the source of the contamination is China.

Chinese Embassy officials strongly objected to the FDA's statements that Chinese companies are to blame, suggesting instead that the problem began in the U.S. At a press conference Monday morning, Chinese health officials said they intend to visit a heparin plant in New Jersey this week.

"The over-sulfated chondroitin cannot be the root cause," of the problems," said Jin Shaohong, deputy director general for the National Institute for the Control of Pharmaceutical and Biological Products in China.



The FDA disputed China's contention that the contaminant hasn't been definitely linked to allergic reactions. "We are aware that our Chinese colleagues are skeptical that such a link has been established," Dr. Woodcock said.

An uproar over tainted drugs, pet food, toothpaste, catfish and

DOW JONES REPRINTS

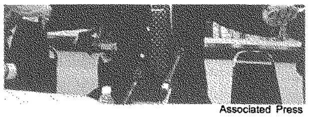
R This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues, clients or customers, use the Order Reprints tool at the bottom of any article or visit: www.djreprints.com.

- See a sample reprint in PDF format.
- Order a reprint of this article now.

FURTHER READING

- Economic Fraud Suspected in Heparin Case[2]
04/16/08
- FDA Identifies Contaminant in Heparin Batches[3]
03/20/08
- Heparin Faces Tougher Testing[4]
03/15/08
- Heparin Contaminant Is Found[5]
03/06/08
- China Says Drug Checks Are Up to Importers[6]
02/28/08
- Gaps Found in Chinese Drug Supply Chain[7]
02/21/08

lead-painted children's toys from China has led to Congressional demands for legislation tightening regulation of food and drug imports and more-aggressive FDA inspection of Chinese facilities shipping food and medicine to the U.S. The U.S. pharmaceutical industry is troubled by the prospect of tougher regulation of imports, because of the potential impact on cheap drug-manufacturing centers.


Associated Press
Jin Shaohong, deputy director general of China's National Institute for the Control of Pharmaceutical and Biological Products, raised doubts over the cause of allergic reactions related to heparin.

The methods China uses to screen for contaminants may be one of the keys to the differences between the FDA's and China's contradictory assessments. The Chinese tests aren't as selective or sensitive and don't effectively detect small amounts of the contaminant, the FDA's Mohed Nasr said.

A major seller of medical heparin, Deerfield, Ill.-based **Baxter International** Inc., has recalled many batches of the product. Warnings or recalls have been issued in Japan, Australia and several European countries.

Chinese officials said noncontaminated heparin lots had been linked to 100 adverse events, 25 of them serious. The FDA said that China's analysis was wrong and that the batch the Chinese tested was later found to be tainted.

Baxter also disagreed with Chinese statements. "The contaminant is present in the batches in which we've received adverse-reaction reports," Baxter spokeswoman Erin Gardiner said.

China's public-relations move against the FDA coincided with the FDA issuing a warning letter to a major Chinese heparin manufacturer, Changzhou SPL, saying the company had "deficiencies" in its response to earlier concerns expressed by the FDA about conditions at its plant. Changzhou SPL is jointly-owned by Scientific Protein Laboratories LLC of Waunakee, Wis., Baxter's main supplier of heparin.

"We do not believe that the warning letter reflects Changzhou SPL's actual state of compliance with current good manufacturing practices" of heparin, the company said. The FDA has said the contaminant seems to have entered the chain prior to Changzhou SPL's involvement.

The Chinese government's response follows comments last week by FDA Commissioner Andrew Von Eschenbach in testimony before a Senate panel that contaminants had been deliberately introduced into numerous lots of heparin during manufacturing and that the adulteration was done to stretch the drug supply at its source for economic gain.

Secretary of Health and Human Services Mike Leavitt told reporters Monday that "cooperation with China has been good" on the agreements the U.S. and China signed in December, which have placed a greater burden on Beijing to regulate exports of food, drugs and medical devices. "There will be disagreements, but despite that, we are working in a productive way," Mr. Leavitt said.

Tuesday, the House Committee on Energy and Commerce was to hold a hearing over gaps in the FDA's oversight of foreign food and drug imports. The new controversy with Chinese health officials will likely surface, as the commissioner of the FDA is among those scheduled to testify.

Carbohydrate Research, 158 (1986) 183–190
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CHEMICAL SULFATION OF PREPARATIONS OF CHONDROITIN 4- AND 6-SULFATE, AND DERMATAN SULFATE. PREPARATION OF CHONDROITIN SULFATE E-LIKE MATERIALS FROM CHONDROITIN 4-SULFATE

KINZO NAGASAWA*, HIDEKI UCHIYAMA, AND NORIE WAJIMA
School of Pharmaceutical Sciences, Kitasato University, 9-1, Shirokane 5 chome, Minato-ku, Tokyo 108 (Japan)

(Received February 10th, 1986; accepted for publication, April 1st, 1986)

ABSTRACT

A solution of the tributylammonium salts of chondroitin 4- or 6-sulfate, or dermatan sulfate in *N,N*-dimethylformamide was treated with 2.0–8.0 mol/hydroxyl group of pyridine–sulfur trioxide at 0° for 1 h. The progress of the sulfation was studied by chondroitinase ABC digestion and liquid chromatography. The results suggested that sulfation proceeded homogeneously according to the order of reactivity of the hydroxyl groups. Various chondroitin polysulfates, which resemble natural chondroitin sulfate E with respect to the disaccharide unit composition, were prepared from chondroitin 4-sulfate.

INTRODUCTION

The present study was initiated to establish the order of reactivity toward sulfation of the hydroxyl groups of chondroitin 4- and 6-sulfate (C-4-S and C-6-S), and of dermatan sulfate, and to develop a method for preparing polysulfated derivatives of these polysaccharides. To achieve this, (a) sulfation must be carried out in completely homogeneous medium[1,2], (b) the progress of the sulfation must be easily controllable, and (c) it must be free from side reactions, such as cleavage or transfer of the glycosidic linkages and decomposition of the sugar components. Recently, we devised a sulfation procedure that satisfies to some degree these requirements, and we report herein the preparation of chondroitin sulfate E-like materials.

RESULTS AND DISCUSSION

Commercial C-4-S and -6-S were successively purified by ion-exchange chromatography on AG 1-X2 anion-exchange resin and by gel filtration on

---

*To whom correspondence should be addressed.

0008-6215/86/$ 03.50 © 1986 Elsevier Science Publishers B.V.

Sepharose 6B gel, respectively. The rooster-comb dermatan sulfate, RC-20 fraction[3], was fractionated by ion-exchange chromatography to obtain the fractions eluted with 2.0M sodium chloride on Dowex 1-X2 (Cl^-) anion-exchange resin. The K_{av} values obtained by analytical gel-filtration of these purified materials on Sepharose 6B were 0.41, 0.31, and 0.31 for C-4-S and -6-S, and dermatan sulfate, respectively. The composition of chondroitinase ABC digestion products and sulfur content are reported in Tables I–III.

As shown in Table I, the starting C-4-S used was a copolymer consisting mainly of chondroitin 4-sulfate (81%) and 6-sulfate units (17%). The tributylammonium salt was treated with 2.0–8.0 mol/mol equiv. of hydroxyl group of

TABLE I

ANALYTICAL DATA OF SULFATED PRODUCTS OF CHONDROITIN 4-SULFATE

Composition	*Starting chondroitin 4-sulfate*	*Sulfated chondroitin 4-sulfate*				*Chondroitin sulfate E*[b]
		Prep. I (2.0)[a]	*Prep. II (4.0)*	*Prep. III (6.0)*	*Prep. IV (8.0)*	
S content (mol/repeating unit)	1.02	1.26	1.60	1.72	2.04	1.55
Unsaturated disaccharide composition (%)						
ΔDi	1.3	0.8	0.4	0.3	0.2	0
ΔDi-6*S*	17.0	17.0	17.1	17.1	13.8	8.0
ΔDi-4*S*	81.0	70.1	33.2	17.9	10.6	30.0
ΔDi-diS_D	0.7	0.4	1.1	1.5	2.1	0
ΔDi-diS_E	0	11.7	48.2	58.4	66.0	62.0
ΔDi-tri*S*	0	0	0	4.8	7.3	

[a] Mol of pyridine–sulfur trioxide per mol equivalent of available hydroxyl group. [b] Ref. 7.

TABLE II

ANALYTICAL DATA OF SULFATED PRODUCTS OF CHONDROITIN 6-SULFATE

Composition	*Starting chondroitin 6-sulfate*	*Sulfated chondroitin 6-sulfate*		
		Prep. I (3.0)[a]	*Prep. II (5.0)*	*Prep. III (7.0)*
S content (mol/repeating unit)	1.08	1.17	1.29	1.48
Unsaturated disaccharide composition (%)				
ΔDi	1.3	0.9	0	0
ΔDi-6*S*	73.9	74.6	74.0	72.3
ΔDi-4*S*	17.7	14.1	2.6	0.8
ΔDi-diS_D	7.1	7.1	8.5	9.9
ΔDi-diS_E	0	3.3	13.8	14.9
ΔDi-tri*S*	0	0	1.1	2.1

[a] See footnote to Table I.

TABLE III

ANALYTICAL DATA OF SULFATED PRODUCTS OF DERMATAN SULFATE

Composition	*Starting dermatan sulfate*	*Sulfated dermatan sulfate*		
		Prep. I (2.0)[a]	*Prep. II (4.0)*	*Prep. III (6.0)*
S content (mol/repeating unit)	1.04	1.27	2.01	2.29
Unsaturated disaccharide composition (%)				
ΔDi	4.4	2.5	1.7	0
ΔDi-6S	3.0	4.4	1.4	1.5
ΔDi-4S	84.2	70.8	28.3	9.2
ΔDi-diS_D	0.6	1.6	4.3	6.0
ΔDi-diS_B	7.0	4.4	2.3	0
ΔDi-diS_E	0.8	14.6	56.4	76.9
ΔDi-tri$S$	0	1.7	5.6	6.4

[a] See footnote to Table I.

pyridine–sulfur trioxide in *N,N*-dimethylformamide at 0° for 1 h in homogeneous solution. The progress of sulfation was dependent on the amount of pyridine–sulfur trioxide used. The progress of the sulfation was monitored by digesting Preparations I–IV (Table I) with chondroitinase ABC and analyzing the digestion products by liquid chromatography under elevated pressure (l.c.)[4]. The data clearly showed the most important process to be the transformation of chondroitin 4-sulfate into chondroitin 4,6-disulfate units; for Preparation II, 60% of the chondroitin 4-sulfate units of the starting material were transformed into chondroitin 4,6-disulfate units without any change of the structure of other disaccharide units. On the contrary, transformation of chondroitin 6-sulfate units into chondroitin 4,6-disulfate units did not occur under the conditions used for Preparations I and II, although chondroitin 6-sulfate units were partially transformed into chondroitin disulfate (D type) units and chondroitin trisulfate units under the reaction conditions used for Preparation IV. These results suggest that the 6-sulfate group on the 2-acetamido-2-deoxy-D-galactose residue of the chondroitin 6-sulfate unit may prevent the 4-HO group on the same monosaccharide residue from undergoing sulfation.

As shown in Table I, the decrease of ΔDi-4S[*] of Preparations I and II well correspond to the respective increase of ΔDi-diS_E. The decrease of ΔDi-4S of

---

[*] Abbreviations used: ΔDi, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid)-D-galactose; ΔDi-4S, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid)-D-galactose 4-sulfate; ΔDi-6S, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid)-D-galactose 6-sulfate; ΔDi-diS_D, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid 2- or 3-sulfate)-D-galactose 6-sulfate; ΔDi-diS_B, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid 2- or 3-sulfate)-D-galactose 4-sulfate; ΔDi-DiS_E, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid)-D-galactose 4,6-bis(sulfate); ΔDi-tri$S$, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid 2- or 3-sulfate)-D-galactose 4,6-bis(sulfate); ΔDi-US, 2-acetamido-2-deoxy-3-*O*-(4-deoxy-α-L-*threo*-hex-4-enopyranosyluronic acid 2- or 3-sulfate)-D-galactose.

Preparation III correspond to the sum of the increase of ΔDi-diS_E and ΔDi-tri$S$ (%). These results strongly suggest that the chondroitin trisulfate unit was preferentially formed by sulfation of the chondroitin 4,6-disulfate (E type) unit, and not by that of the chondroitin disulfate (D type) unit.

As shown in Table II, C-6-S was more difficult to sulfate than C-4-S. This seems to be exclusively due to the marked resistance of the chondroitin 6-sulfate unit against further sulfation, as the data suggest that the proportion of chondroitin 6-sulfate units remains unchanged in Preparations I–III, and the increase in sulfur content depends mostly on the transformation of the chondroitin 4-sulfate units present in chondroitin 4,6-disulfate units. These data also indicate that a limited proportion of the chondroitin 6-sulfate units underwent sulfation to give chondroitin disulfate (D type) units. Accordingly, more drastic reaction conditions would result in the formation of additional chondroitin disulfate (D type) units and chondroitin trisulfate units as suggested by the results obtained previously[5].

Subsequently, a preparation of rooster-comb dermatan sulfate was subjected to sulfation under the same conditions as just described. The preparation of dermatan sulfate investigated contained more disaccharide 4-sulfate and less disaccharide 6-sulfate units than the preparation of C-4-S. As shown in Table III, the sulfation of the polysaccharide was very similar to that of C-4-S, indicated by the preponderant transformation of disaccharide 4-sulfate into the disaccharide 4,6-disulfate units. The data also show a slow but steady transformation of the disaccharide disulfate (B type) into disaccharide trisulfate units for Preparations I–III, suggesting that HO-6 of the 2-acetamido-2-deoxy-D-galactose residue of the disaccharide disulfate (B type) units is highly sensitive to sulfation under the reaction conditions used. Comparison between Tables I and III revealed that the sulfated products of dermatan sulfate were more sulfated than those of C-4-S, owing in part to the preponderance of unsubstituted HO-6 groups in the disaccharide units of dermatan sulfate (Table III), as compared with C-4-S (Table I), and in part to some difference in the three-dimensional structures of both starting materials.

A sulfated C-4-S obtained by the present method (Preparation IV in Table I) was digested with chondroitinase ABC alone or chondroitinase ABC plus chondrosulfatases, and each digestion product was analyzed for unsaturated disaccharide composition by l.c. (Table IV). The data suggest that ΔDi-tri$S$ was produced by chondroitinase ABC digestion of a disaccharide trisulfate unit, in which one sulfate group is located either at O-2 or -3 of the 4,5-unsaturated uronic acid residue and the other two sulfate groups at O-4 and -6 of the acetamido-2-deoxy-D-galactose residue.

The data of Tables I–III indicate that the sulfation progressed homogeneously according to the order of reactivity of the hydroxyl groups within the polysaccharide molecules. A gel-filtration analysis of Preparation III (Table I) did not show any scission of the polysaccharide chain (Fig. 1).

A chondroitin polysulfate (ChS-E), isolated from squid cranial cartilage[6,7], has been shown to have physiological roles in mammals[8–11]. The data in Table I

TABLE IV

UNSATURATED DISACCHARIDE COMPOSITION OF DIGESTION PRODUCTS GENERATED FROM SULFATED CHONDROITIN 4-SULFATE WITH CHONDROITINASE ABC ALONE, OR CHONDROITINASE ABC PLUS CHONDROSULFATASES

Unsaturated disaccharide composition (%)	*Digestion product of sulfated chondroitin 4-sulfate*[a] *with enzyme(s)*		
	Chondroitinase ABC alone[b]	*Chondroitinase ABC plus chondro-6-sulfatase*	*Chondroitinase ABC plus chondro-6- and -4-sulfatases*
ΔDi	0.2	14.4	90.7
ΔDi-U*S*	0	2.1	9.3
ΔDi-6*S*	13.8	0	0
ΔDi-4*S*	10.6	75.5	0
ΔDi-diS_D	2.1	0	0
ΔDi-diS_B	0	8.0	0
ΔDi-diS_E	66.0	0	0
ΔDi-tri*S*	7.3	0	0

[a] Preparation IV in Table I. [b] Data from Table I.

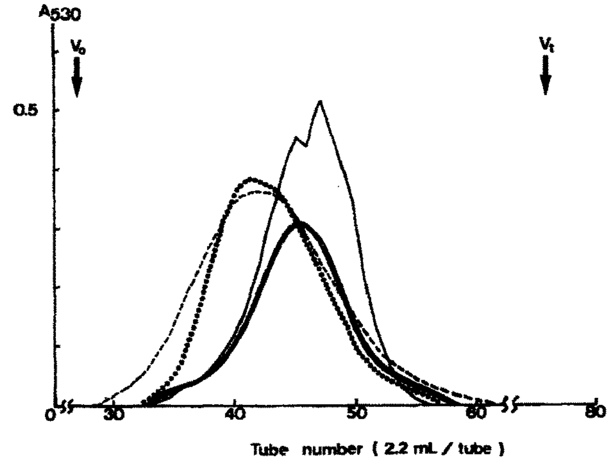


Fig. 1. Elution diagrams of starting chondroitin 4- and 6-sulfate and dermatan sulfate, and of sulfated chondroitin 4-sulfate on Sepharose 6B: (——) chondroitin 4-sulfate, (----) chondroitin 6-sulfate, (●●●●●●●) dermatan sulfate, and (——) sulfated chondroitin 4-sulfate (Preparation III, Table I).

suggest that several chondroitin polysulfates, which possess a similar degree of disaccharide unit composition as those of natural ChS-E preparations[8–11], may be obtained by sulfation of C-4-S. Thus, a sufficient supply of semi-synthetic ChS-E preparations will contribute to the study of the physiological functions of ChS-E.

EXPERIMENTAL

Materials. — Chondroitin 4-sulfate (whale cartilage, reagent grade) and chondroitin sulfate (shark cartilage, reagent grade), chondroitinase ABC from *Proteus vulgaris* (chondroitin sulfate lyase, EC 4.2.99.6), chondro-4- and -6-sulfatases from *Proteus vulgaris,* and 4,5-unsaturated disaccharide standards (ΔDi, ΔDi-4*S*, and ΔDi-6*S*) were obtained from Seikagaku Kogyo Co. Ltd. (Tokyo). The chondroitin 4-sulfate was further purified by ion-exchange chromatography on AG 1-X2 (Cl^-) resin with a linear gradient elution of 1.5–2.5M NaCl. The fraction eluted with 1.52–1.66M NaCl was used for the present experiments. A preparation of rooster-comb dermatan sulfate[3] (RC-20) was fractionated into 1.5 and 2.0M NaCl fractions by ion-exchange chromatography on Dowex 1-X2 (Cl^-) resin, and the 2.0M NaCl fraction, a dermatan sulfate–chondroitin sulfate copolymer having an IdoA/GlcA ratio of 41:9, was used for the present experiments. The elution diagrams of these starting materials on Sepharose 6B gel are shown in Fig. 1. Pyridine–sulfur trioxide obtained from Aldrich Chem. Co. Inc. (Milwaukee, Wis 53201) was purified according to the procedure described[12].

Analytical methods. — The uronic acid content was determined by the modified method of Bitter and Muir[13,14]; the uronic acid composition of the dermatan sulfate by the procedure previously described[3]; and the sulfur content by the method of Dodgson and Price[15]. Analytical gel-chromatography on Sepharose 6B was carried out by the same procedure described previously[16], modified by increasing the NaCl concentration to 0.2M.

Determination of constitutional disaccharide composition in chondroitin 4- and 6-sulfate, and dermatan sulfate, and their sulfated products. — The determination was carried out according to the procedure of Seldin *et al.*[4]. To a solution of the sample (200 μg) in water (40 μL) were added 50mM Tris·HCl buffer (pH 8.0, 20 μL) containing 10mM NaF, and chondroitinase ABC (0.4 unit) in water (40 μL), and the mixture was incubated for 2 h at 37°. It was diluted with ethanol (4 vol.), cooled to 0° for 2 h, and centrifuged at 5500 *g* for 15 min. The supernatant (0.45 mL) was evaporated under a stream of nitrogen, and the residue dissolved in l.c. solvent *A* (3:1, v/v, 70% acetonitrile–methanol and 30% 0.2M ammonium acetate–acetic acid, pH 5.3) (36 μL). L.c. was performed with a chromatographic apparatus equipped with a liquid delivery pump (NP-D, 5SK25GK-A, Oriental motor Co., Tokyo), a variable-wavelength u.v. detector (S-310A model-II, Nihonseimitsu Co., Tokyo), a Whatman Partisil-10 PAC column (4.6 × 250 mm), and a precolumn (4.6 × 25 mm) containing the same packing. The u.v. absorbance of the column eluate was monitored with a detector at 232 nm. The unsaturated disaccharide (ΔDi) and unsaturated disaccharide monosulfates (ΔDi-4*S*, ΔDi-6*S*, and ΔDi-U*S*) were eluted with solvent *A*. The unsaturated disaccharide disulfates (ΔDi-diS_B, ΔDi-diS_D, and ΔDi-diS_E) and unsaturated disaccharide trisulfate (ΔDi-tri*S*) were eluted with solvent *B* (3:1, v/v, 70% acetonitrile–methanol and 30% 0.4M ammonium acetate–acetic acid, pH 5.3) and solvent *C* (3:1, v/v, 65% acetonitrile–methanol and 35% 0.55M sodium acetate–acetic acid, pH 5.3), respectively. The peaks of ΔDi, ΔDi-4*S*, and ΔDi-6*S* were assigned by comparison with the retention times of commercial standards. Each peak of the unsaturated disaccharide di- and tri-sulfates was assigned by comparison of the chromatographic data of each digestion product of the same sample with chondro-4- and chondro-6-sulfatase with those of reference samples (ΔDi, ΔDi-4*S*, and ΔDi-6*S*). The conditions of sulfatase digestion were as follows. To a solution of the sample (200 μg) in enriched Tris buffer[17] [0.3M sodium acetate, 0.25M NaCl, 0.25M Tris·HCl (pH 8.0), and bovine serum albumin (0.5 mg/mL)] (40 μL) was added chondroitinase ABC (0.4 unit) in water (20 μL). The mixture was incubated for 2 h at 37°, and then chondro-6-sulfatase (0.8 unit) in water (40 μL) alone, or chondro-4- and -6-sulfatases (each 0.8 unit) in water (40 μL) were added, and the incubation was continued for additional 16 h at 37°. The mixture was diluted with ethanol (4 vol.), cooled to 0° for 2 h, and centrifuged at 5500 *g* for 20 min. The precipitate was resuspended in water (0.1 mL) and the mixture centrifuged at 5500 *g* for 20 min. The combined supernatants were evaporated under a stream of N_2. The residue was dissolved in solvent *A* (40 μL) and analyzed by l.c. with the same solvent and the 4,5-unsaturated disaccharide standards (ΔDi, ΔDi-4*S*, and ΔDi-6*S*) as reference.

Sulfation of chondroitin 4- and 6-sulfates, and dermatan sulfate. — A solution of the Na salt of each polysaccharide ($\sim$50 mg) in water (5 mL) was passed through a column of Dowex 50W-X8 (H$^+$, 50–100 mesh) at 0°, and the pH of the effluent was adjusted to 5.0 by the addition of 10% tributylamine in ethanol. The solution was extracted three times with diethyl ether (each 50 mL) and lyophilized to give the tributylammonium salt ($\sim$50 mg) as a white powder.

To a solution of the tributylammonium salt of each polysaccharide ($\sim$6 mg) in *N,N*-dimethylformamide (0.5 mL) was added a solution of pyridine–sulfur trioxide (2.0–8.0 mol/equiv. of available hydroxyl group) in *N,N*-dimethylformamide (0.5 mL), and the mixture was stirred for 1 h at 0°. The reaction was terminated by the addition of cold water (1 mL) and the pH of the solution was adjusted to 9.0 with M NaOH. The solution was diluted with ethanol (3 vol.) saturated with anhydrous sodium acetate and kept for 1 h at 0° to give a white precipitate. The precipitate was collected by centrifugation at 1500 *g* for 15 min and dissolved in a small volume of water. The solution was dialyzed against distilled water (3 × 20 L) for 20 h and the dialyzate lyophilized to give the sodium salt of the sulfated product (4–5 mg) as a white powder.

REFERENCES

1 E. E. Gilbert, *Sulfonation and Related Reactions, Interscience,* New York, 1965, pp. 354–360.
2 J. F. Kennedy, *Adv. Carbohydr. Chem. Biochem.*, 29 (1974) 305–405.
3 K. Nagasawa, A. Ogamo, H. Ichihara, and K. Yoshida, *Carbohydr. Res.*, 131 (1984) 301–314.
4 D. C. Seldin, N. Seno, K. F. Austen, and R. L. Stevens, *Anal. Biochem.*, 141 (1984) 291–300.
5 A. Ogamo, A. Nagai, and K. Nagasawa, *Biochim. Biophys. Acta,* 841 (1985) 30–41.
6 Y. Kawai, N. Seno, and K. Anno, *J. Biochem. (Tokyo)*, 60 (1966) 317–321.
7 S. Suzuki, H. Saito, T. Yamagata, K. Anno, N. Seno, Y. Kawai, and T. Furuhashi, *J. Biol. Chem.*, 243 (1968) 1543–1550.
8 E. Razin, R. L. Stevens, F. Akiyama, K. Schmid, and K. F. Austen, *J. Biol. Chem.*, 257 (1982) 7229–7236.
9 Y. Hojima, C. G. Cochrane, R. C. Wiggins, K. F. Austen, and R. L. Stevens, *Blood,* 63 (1984) 1453–1459.
10 L. Enerbäck, S. O. Kolset, M. Kusche, A. Hjerpe, and U. Lindahl, *Biochem. J.*, 227 (1985) 661–668.
11 S. Kobayashi, K. Oguri, E. Yaoita, K. Kobayashi, and M. Okayama, *Biochim. Biophys. Acta,* 841 (1985) 71–80.
12 P. Baumgarten, *Ber. Dtsch. Chem. Ges.*, 59 (1926) 1166–1171.
13 T. Bitter and H. M. Muir, *Anal. Biochem.*, 4 (1962) 330–334.
14 M. Kosakai and Z. Yosizawa, *Anal. Biochem.*, 93 (1979) 295–298.
15 K. S. Dodgson and R. G. Price, *Biochem. J.*, 84 (1962) 106–110.
16 H. Uchiyama, A. Ogamo, and K. Nagasawa, *Carbohydr. Res.*, 99 (1982) 87–92.
17 H. Saito, T. Yamagata, and S. Suzuki, *J. Biol. Chem.*, 243 (1968) 1536–1542.

ELSEVIER

Carbohydrate Research 306 (1998) 35–43

CARBOHYDRATE
RESEARCH

Conformational changes and anticoagulant activity of chondroitin sulfate following its *O*-sulfonation [1]

Tomohiro Maruyama [a], Toshihiko Toida [a], Toshio Imanari [a,*],
Guyong Yu [b], Robert J. Linhardt [b]

[a] *Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263, Japan*
[b] *Departments of Chemical and Biochemical Engineering, and Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA 52242, USA*

Received 28 July 1997; accepted 10 October 1997

Abstract

Chondroitin sulfate from bovine tracheal cartilage, with the basic structure (4-*O*-sulfo-D-Gal*p*NAcβ1 → 4-D-Glc*p*A)$_n$, was chemically modified by *O*-sulfonation. Depending on the reaction conditions, the products showed a different degree of *O*-sulfonation. A fully *O*-sulfonated chondroitin sulfate, having no free hydroxyl groups, and a sulfo ester group:disaccharide unit ratio of 4.0 was prepared. This chondroitin sulfate derivative was shown by ^{1}H NMR spectroscopy to have a uronate residue with an altered conformation. Usually, the uronate residue in chondroitin sulfate resides in the ${}^4C_1$ form. Fully *O*-sulfonated chondroitin sulfate had an uronate residue in the ${}^1C_4$ form at 30 °C, similar to the preferred conformation of the 2-*O*-sulfo-iduronate residue most commonly found in heparin. The ${}^2S_0$ form of the uronate residue was also found in fully *O*-sulfonated chondroitin sulfate at 60 °C. The anti-factor IIa activity of fully *O*-sulfonated chondroitin sulfate was 40 units/mg. This value is similar to the activities reported for various low-molecular-weight heparins, and substantially higher than those previously reported for partially *O*-sulfonated chondroitin sulfates having an average sulfate group/disaccharide unit of 2.5 to 3.3. The anti-factor Xa activity of the fully *O*-sulfonated chondroitin sulfate was 12 units/mg. This value is considerably lower than the activities reported for various low-molecular-weight heparins, consistent with the critical importance of an antithrombin III pentasaccharide binding site for anti-factor Xa activity. These findings suggest that the conformational change of glucuronic acid residue in

---

[*] Corresponding author. Tel.: +81-43-290-2894; fax: +81-43-290-3021; e-mail: imanari@p.chiba.u.ac.jp.

[1] Abbreviations: GAG(s), glycosaminoglycan(s); Glc*p*A, D-glucuronic acid; Glc*p*A2S, 2-*O*-sulfo-D-glucuronic acid; Glc*p*A3S, 3-*O*-sulfo-D-glucuronic acid; Gal*p*N, D-galactosamine; Ac, acetyl; PAGE, polyacrylamide gel electrophoresis; GPC, gel-permeation chromatography; TBA, tributylammonium; TBA · SO_3, tributylamine-sulfur trioxide; Py · SO_3, pyridine-sulfur trioxide; ATIII, antithrombin III; HCII, Heparin cofactor II; NHP, normal human plasma; 1D, one-dimensional; 2D, two-dimensional

0008-6215/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.

chondroitin sulfate resulting from its full *O*-sulfonation can result in enhanced anticoagulant activity, particularly as measured by anti-factor IIa assay. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Chemical oversulfonation; Chondroitin sulfate; Anticoagulant activity; Conformational change; ^{1}H NMR spectroscopy

---

1. Introduction

Chondroitin sulfates are families of structurally complex, sulfated, linear polysaccharides called glycosaminoglycans (GAGs) with alternating D-glucuronic acid (Glc*p*A) and *N*-acetylated D-galactosamine (Gal*p*NAc) residues [1]. Chondroitin sulfates contain, on average, one sulfate group per disaccharide unit at either the C-4 or C-6 positions of GalNAc [1]. This polysaccharide is part of proteoglycans found localized on cell surfaces and in the extracellular matrix and is important in cell–cell communication [1–3]. While chondroitin sulfates appear to be involved in maintaining hemostasis [4], chondroitin sulfates lack clinically relevant levels of anticoagulant activity, presumably the result of their structural differences from the clinical anticoagulant heparin, including their low level of sulfation [5].

Heparin has been the drug of choice in clinical, pre-surgical and post-surgical prophylaxis of thrombotic events [6]. However, because of its side effects, such as bleeding and other disadvantages, developing alternatives to heparin is an important research goal [7]. Recently, other polysaccharides and modified polysaccharides have been examined as potential heparin analogs in drug development [6,8]. Oversulfated chondroitin sulfates with two to three sulfate groups per disaccharide unit have been shown to exhibit enhanced antithrombotic activity [9]. These chemically prepared oversulfated chondroitin sulfates still contain glucuronic acid residues, making them both structurally and conformationally different from the iduronic acid residues found in heparin [10,11].

In this paper, chondroitin sulfate is completely *O*-sulfonated, and the solution conformations of its glucuronate residues are examined using ^{1}H NMR spectroscopy. The relationship between the conformation of the glucuronic acid residues and anticoagulant activity is discussed.

2. Results

Preparation and characterization of chemically oversulfated chondroitin sulfates.—Chemical *O*-sulfonation reactions of bovine tracheal cartilage chondroitin sulfate at different temperatures resulted in oversulfated chondroitin sulfates having different levels of sulfation. Gradient polyacrylamide gel electrophoresis (PAGE) analysis [12] (data not shown) of each sample was undertaken to determine molecular weight. In addition to showing a slight increase in molecular weight on *O*-sulfonation, the microheterogeneity of the sample of the partially *O*-sulfonated sample increases as shown by a reduction in clearly defined banding on gradient PAGE analysis. Gel-permeation chromatography (GPC) [13] also showed an expected small increase in molecular weight concomitant with increased level of sulfation. These results are consistent with the added mass of the *O*-sulfo groups as well as the stability of the glycosidic linkages in the polysaccharides under the reaction conditions. Sulfate analysis of chondroitin sulfate and oversulfated chondroitin sulfates prepared at 0 °C and at 40 °C are consistent with 1, 2.5–3.3 and 4 *O*-sulfo groups/disaccharide repeating unit.

A disaccharide compositional analysis of the partially and fully *O*-sulfonated chondroitin sulfate was attempted by exhaustive treatment chondroitin sulfate lyases ABC/ACII, followed by HPLC analysis, to confirm that *O*-sulfonation had taken place. The recoveries of the unsaturated disaccharides from partially oversulfated chondroitin sulfate were decreased depending on the sulfation degree. In the case of the fully *O*-sulfonated chondroitin sulfate sample, no unsaturated disaccharide products were detected (data not shown). This result was expected based on the known resistance of oversulfated domains to these enzymes [14].

IR spectra of the chondroitin sulfate and fully *O*-sulfonated chondroitin sulfate (data not shown) strongly suggest the conversion of hydroxy groups to axial *O*-sulfonate groups. The intensity of the absorbances at 1240 cm^{-1} and 820–850 cm^{-1} attributed to the stretching of S=O bond and C–O–S bonds, respectively, are dramatically increased by *O*-sulfonation. Similarly, the intensity of the bands at 2900, 1440, 1380 and 1100 cm^{-1}, attributed to the stretching and/or deformation vibration of C–O–H

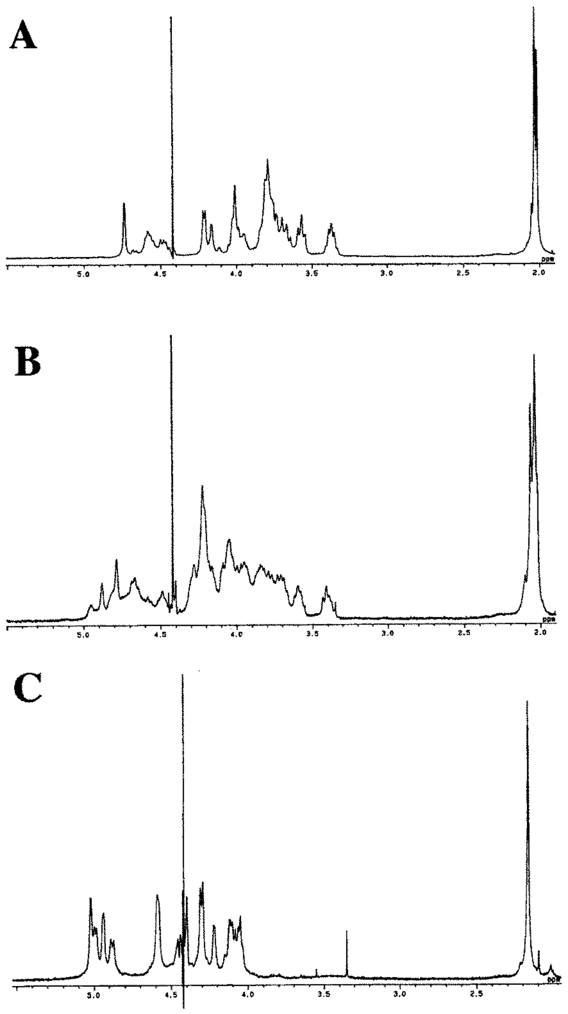


Fig. 1. One-dimensional ^{1}H NMR spectra of chondroitin sulfate and chemically *O*-sulfonated chondroitin sulfates measured at 303 K. (A) Intact bovine tracheal chondroitin sulfate; (B) partially *O*-sulfonated ($SO_3H/COOH = 3.2$) chondroitin sulfate prepared from bovine tracheal chondroitin sulfate; (C) fully *O*-sulfonated chondroitin sulfate ($SO_3H/COOH = 4.0$).

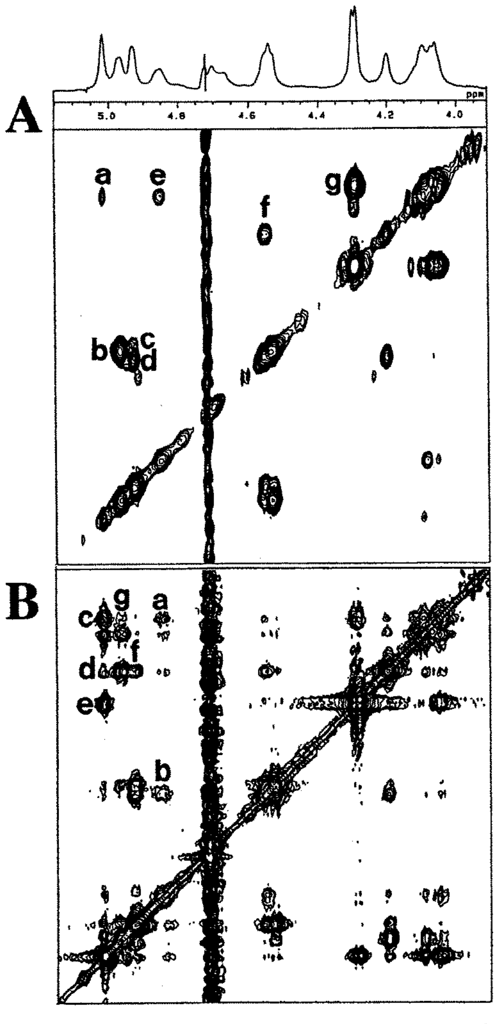


Fig. 2. Two-dimensional DQF-COSY and NOESY spectra of fully *O*-sulfonated chondroitin sulfate measured at 333 K. (A) DQF-COSY spectrum; (B) NOESY spectrum of fully *O*-sulfonated chondroitin sulfate. *Cross peaks (upper panels)*: (a) Gal*p*NAc H-3/H-4; (b) Glc*p*A H-1/H-2; (c) Glc*p*A H-2/H-3; (d) Glc*p*A H-3/H-4; (e) Gal*p*NAc H-1/H-2; (f) Glc*p*A H-4/H-5; (g) Gal*p*NAc H-5/H-6: (*lower panel*) (a) Gal*p*NAc H-1/H-3; (b) Gal*p*NAc H-1/Glc*p*A H-4; (c) Gal*p*NAc H-4/H-5; (d) Gal*p*NAc H-4/Glc*p*A H-5; (e) Gal*p*NAc H-4/H-6; (f) Glc*p*A H-3/H-5; (g) Glc*p*A H-1/Gal*p*NAc H-3.

Table 1
Chemical shifts (ppm) and coupling constants (Hz) of fully *O*-sulfonated chondroitin sulfate

Residue probe temperature	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}$	H-6	N–Ac
Gal*p*NAc							
333 K	4.88	4.11	4.11	5.02	4.05	4.30	2.17
	7.1	n.d.[a]	n.d	< 1.5	6.1		
303 K	4.86	4.10	4.10	5.02	4.06	4.29	2.16
	7.4	n.d.	n.d.	< 1.5	6.2		
Glc*p*A							
333 K	5.00	4.59	4.94	4.59	4.23	–	–
	5.9	n.d.	< 1.5	< 1.5			
303 K	4.97	4.53	4.94	4.55	4.20		
	< 1.5	< 1.5	< 1.5				

[a] Not determined.

bonds, are decreased in the spectrum of the fully *O*-sulfonated chondroitin sulfate.

Assignments of IR absorption bands at 1240 cm^{-1} [15], and 1430 cm^{-1} were based on reports by Casu et al. [16], and bands in the 820–850 cm^{-1} spectral region were attributed to C–O–S stretching based on the results of the work of Orr [17]. Multiple bands at about 800–820 cm^{-1} were tentatively ascribed to sulfate half-ester based on the report of Grant et al. [18], and the band at 800 cm^{-1} was ascribed to C–O–S stretching within predominantly axial 2-*O*- and 3-*O*-sulfo groups of glucuronate residues based on the work of Sanderson et al. [19].

A change in the optical rotation of chondroitin sulfate from −30° to −8° accompanies its full *O*-sulfonation. In the case of partially oversulfated samples, the difference of the optical rotation from the intact chondroitin sulfate was not so significant (data not shown). The magnitude and direction of this change is consistent with a significant change in the molecular conformation of these derivatives. These observations suggest that the most important factor in the optical rotational change is not the degree of *O*-sulfonation but rather the result of conformational change [18].

One-dimensional (1D) ^{1}H NMR spectra of chondroitin sulfate and *O*-sulfonated chondroitin sulfates prepared at 0 °C and 40 °C shown in Fig. 1. The spectra of the parent chondroitin sulfate showed a substantial level of structural heterogeneity resulting from the presence and/or absence of sulfation at the 4- and/or 6-positions of the Gal*p*NAc residue. Chemical *O*-sulfonation at 0 °C shows an expected [20,21] increase in the structural heterogeneity compared to the parent chondroitin sulfate. This increased heterogeneity results from the introduction of addi-

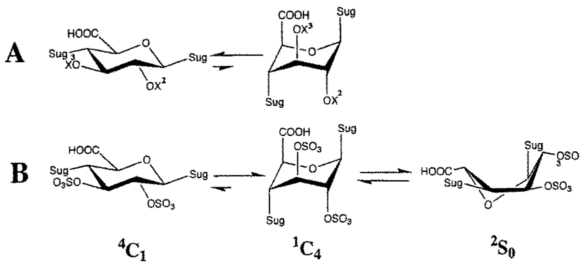


Fig. 3. Effect of the level of *O*-sulfonation on the conformation of the glucuronic acid residue in chondroitin sulfate. (A) The glucuronate residue of partially *O*-sulfonated chondroitin sulfate, where $X^2 = SO_3^-$ and $X^3 = H$ or $X^2 = H$ and $X^3 = SO_3^-$, resides primarily in the $^4C_1$ conformer. (B) The glucuronate residue of fully *O*-sulfonated chondroitin sulfate resides primarily in the $^1C_4$ conformer at 30 °C and in the $^2S_0$ conformer at 60 °C.

tional sulfate groups at the 4- and/or 6-positions of Gal*p*NAc as well as the 2- and/or 3-positions of Glc*p*A. Surprisingly, chemical *O*-sulfonation at 40 °C results in a considerably less complex 1D ^{1}H NMR spectrum, suggesting a reduced structural heterogeneity consistent with full *O*-sulfonation. Two-dimensional (2D) ^{1}H NMR experiments, DQF-COSY and NOESY spectra, of the fully *O*-sulfonated chondroitin sulfate, depicted in Fig. 2, clearly show the downfield shifts of ring protons attached to the *O*-sulfonated carbons, such as Glc*p*A H-2, H-3, and Gal*p*NAc H-4, H-6, and also affords sequence confirmation. The cross peaks detected in NOESY spectrum between Glc*p*A H-1 and Gal*p*NAc H-3, and Gal*p*NAc H-1 and Glc*p*A H-4 strongly suggest that the sequence and linkage positions of the fully *O*-sulfonated chondroitin sulfate are maintained.

The chemical shifts and coupling constants of ring protons of each sample are summarized in Table 1. Based on the Karplus equation, the coupling constant of each ring proton of glucuronate at 30 °C shows that the dihedral angles of vicinal protons of glucuronate are not at 180°, which is typically observed for a glucuronate residue. These data strongly suggest the glucuronate residue has undergone a conformational change from $^{4}C_{1}$ to $^{1}C_{4}$ promoted through the full *O*-sulfonation of this residue (Fig. 3). The coupling constant between H-1 and H-2 of glucuronate residue at 60 °C dramatically changes from < 1.5 to 5.9 Hz (Table 1). These observations strongly suggest that at 60 °C the conformation of the glucuronate residue, in the fully *O*-sulfonated chondroitin sulfate, has changed from $^{1}C_{4}$ to $^{2}S_{0}$ (Fig. 3).

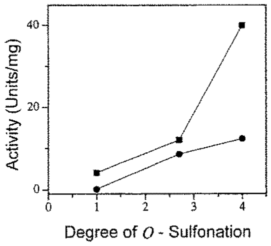


Fig. 4. Effect of the degree of *O*-sulfonation of chondroitin sulfate on the anticoagulant activity. Anti-factor IIa activity (■) and anti-factor Xa activity (●) in units/mg (determined based on a heparin standard curve) are plotted as a function degree of *O*-sulfonation (*O*-sulfonate groups/disaccharide repeating units).

Effect of oversulfated chondroitin sulfate on the inactivation of factor IIa and factor Xa by human plasma.—A correlationship between the sulfation level of chemically *O*-sulfonated chondroitin sulfates and their inactivation of factor IIa activity is shown in Fig. 4. The dependence of the anti-factor IIa anticoagulant activity is clear with a dramatic increase in activity observed for the fully *O*-sulfonated chondroitin sulfate. This dramatic increase on full *O*-sulfonation suggests that the anti-factor IIa activity is not merely the result increased overall charge and that some other structural change, such as a shift in conformation, might be responsible for the high activity observed for the fully *O*-sulfonated chondroitin sulfate derivative. While an increase in anti-factor Xa activity was also observed in the oversulfated chondroitin sulfate derivatives, the magnitude of this increase was considerably less. Thus, the increased anti-factor Xa activity may simply result from a nonspecific effect associated with the overall molecular charge.

3. Discussion

Oversulfated disaccharide sequences have been reported to account for a minor but important part of the structure of chondroitin sulfates derived from mammalian tissues [22,23]. Although chemical *O*-sulfonation of chondroitin sulfate has been previously reported [21], unmodified hydroxyl groups remained, affording a product of high structural heterogeneity as demonstrated from the complexity of both gradient PAGE analysis (data not shown) and the 1D NMR spectrum shown in Fig. 1B. Optimum conditions for complete *O*-sulfonation of chondroitin sulfate were determined to be 40 °C for 1 h with 15 equiv. of sulfonation reagent/mol of hydroxy group. Under these conditions, the molecular weight increased slightly, consistent with the mass of the added *O*-sulfo and the absence of breakdown of the glycosidic linkages (data not shown). Full *O*-sulfonation of chondroitin sulfate is demonstrated by both 1D and 2D ^{1}H NMR experiments (Figs. 1 and 2), by the sulfate analysis data, and by the failure of chondroitin lyases to act on this product.

The present results demonstrate that products obtained by chemical modification of chondroitin sulfate show anti-factor IIa activities (Fig. 4) comparable with the activities displayed by previously described heparin analogs [8] and various low-molecular-weight heparins [6]. Optical rotation measurements suggest a change in conformation, and a band at 800 cm^{-1} in the IR spectra suggest as an axial disposition of the 2- and 3-*O*-sulfo groups in the glucuronate residue (data not shown). NMR spectroscopy (Figs. 1 and 2) demonstrates the conformation of glucuronate residues of a fully *O*-sulfonated chondroitin sulfate derivative is altered from $^4C_1$ to $^1C_4$ at 30 °C (Fig. 3), possibly resulting from the repulsion of negatively charged sulfate groups. This conformational change corresponds to a substantial increase in anti-factor IIa activity (Fig. 4).

The $^1C_4$ conformation of the glucuronate residue in fully *O*-sulfonated chondroitin sulfate closely resembles the 2-*O*-sulfo-iduronate residue commonly found in heparin. Interestingly, the same magnitude of increase is not observed in anti-factor Xa activity. Indeed, while the anti-factor IIa activity of fully *O*-sulfonated chondroitin sulfate is comparable to that of low-molecular-weight heparins, the anti-factor Xa activity is less than 20% of that of low-molecular-weight heparins [6]. These results may be explained by the different protease inhibitors present in plasma that inhibit factor IIa and factor Xa. Factor IIa can be inhibited by both antithrombin III (ATIII) and heparin cofactor II (HCII), while factor Xa is only inhibited by ATIII. While ATIII is known to bind to a specific pentasaccharide sequence found within heparin's structure, HCII binds with considerably less specificity to oversulfated domains of heparin [24], dermatan sulfate, and chondroitin sulfates [25]. Thus, it is likely that the large enhancement of anti-factor IIa activity observed for fully *O*-sulfonated chondroitin sulfate is an HCII-mediated activity.

It is possible that the anticoagulant activity can be further increased by appropriate refinement of the modification procedure for *N*-deacetylation–*N*-desulfonation [26] of fully *O*-sulfonated chondroitin sulfate. These possibilities point to new practically feasible routes for the generation of heparin-like compounds with various pharmacologically relevant biological activities.

4. Experimental

Materials.—Chondroitin sulfate from bovine tracheal cartilage was kindly gifted from Shin-Nippon Yakugyo (Tokyo, Japan). Unsaturated disaccharides [2-acetamido-2-deoxy-3-*O*-(β-D-*threo*-4-hexenopyranosyluronic acid)-D-glucose (ΔDi-HA), 2-acetamido-2-deoxy-3-*O*-(β-D-*threo*-4-hexenopyranosyluronic acid)-D-galactose (ΔDi-0S), 2-acetamido-2-deoxy-3-*O*-(β-D-*threo*-4-hexenopyranosyluronic acid)-6-*O*-sulfo-D-galactose (ΔDi-6S), 2-acetamido-2-deoxy-3-*O*-(β-D-*threo*-4-hexenopyranosyluronic acid)-4-*O*-sulfo-D-galactose (ΔDi-4S), 2-acetamido-2-deoxy-3-*O*-(2-*O*-sulfo-β-D-*threo*-4-hexenopyranosyluronic acid)-4-*O*-sulfo-D-galactose (ΔDi-S$_B$)], and chondroitin lyase ABC (Chase ABC, EC 4.2.2.4) and ACII *arthro* (Chase ACII, EC 4.2.2.5) were purchased from Seikagaku Kogyo (Tokyo, Japan). TSKgel NH$_2$-60 anion-exchange resin (particle size, 5 μm) for HPLC column packing was obtained from Tosoh (Tokyo, Japan). The Asahipak gel-permeation chromatography (GPC) HPLC column was from Asahikasei (Yokohama, Japan).

Preparation of chemically oversulfated chondroitin sulfate.—Chemical *O*-sulfonation to obtain oversulfated chondroitin sulfate was carried out under mild conditions with adducts of sulfur trioxide (SO$_3$) in aprotic solvents [27]. Fully *O*-sulfonated chondroitin sulfate was prepared from the tributylamine (TBA) salt, obtained from 100 mg of chondroitin sulfate, sodium salt by strong cation-exchange chromatography, and concentration by lyophilization. The resulting salt was dissolved in 0.8 mL of *N,N*-dimethylformamide (DMF) to which a required excess (15 mol/equivalent of available hydroxy group in chondroitin sulfate) of pyridine–sulfur trioxide complex had been added. After 1 h at 40 °C, the reaction was interrupted by addition of 1.6 mL of water, and the raw product was precipitated with 3 volumes of cold ethanol saturated with anhydrous sodium acetate, and then collected by centrifugation. The resulting fully *O*-sulfonated chondroitin sulfate was dissolved in water, dialyzed to remove salts, and lyophilized.

Estimation of molecular weight.—The weight average molecular weight of each chondroitin sulfate sample was estimated using gradient PAGE analysis [12]. Determinations were made in a 12–22% gradient mini-gel visualized with Alcian Blue by the method of Edens et al. [12]. The relative molecular weights of each chondroitin sulfate were confirmed by their elution position from a GPC–HPLC column eluted with 50 mM NaOAc, pH 7.4 at a flow rate of 1 mL/min, with detection at 206 nm [13].

HPLC conditions for disaccharide analysis.—The determination of unsaturated disaccharides prepared from intact and modified chondroitin sulfates was performed on chondroitin lyase-digested samples using HPLC [28]. The HPLC conditions were as follows: Injection size 10 to 20 μL (5 μg/mL), on a

TSKgel NH_2-60 column (4.6 mm i.d. × 250 mm length) eluted with 40 mM Tris–borate buffer (pH 7.5 adjusted with HCl) and 7 mM Na_2SO_4 in 54% acetonitrile at a flow rate of 0.5 mL/min. Post-column derivatization was used to detect each unsaturated disaccharide. NaOH solution (0.3 M) and 1% 2-cyanoacetamide solution were delivered to the eluate at a flow rate of 0.25 mL, each controlled by a reciprocated double plunger pump. The mixture was then introduced to a polytetrafluoroethylene (PTFE) reaction coil (0.5 mm i.d. × 10 m) thermostated at 105 °C by using a dry reaction aluminum heating block, then introduced to a PTFE cooling coil (0.25 mm i.d. × 2 m) in water bath. The effluent was monitored by a fluorometric detector (excitation, 346 nm; emission, 410 nm).

Sulfate analysis.—Chondroitin sulfate samples were prepared for the determination of sulfate by exhaustive dialysis against distilled water using MWCO 3500 tubing, lyophilization and drying for 2 days in a desiccator over phosphorus pentoxide. The determination of sulfate group was performed following combustion by HPLC using a conductivity detector, Tosoh model CM-8 (Tokyo, Japan).

IR spectroscopy.—For IR spectroscopy of solid samples, a Jasco model FTIR 230 (Tokyo, Japan) was used. A 100 μg portion of glycosaminoglycan was mixed with 500 μg of dried potassium bromide, pressed, and the resulting salt disc (3 mm diameter) was placed in the spectrometer.

Optical rotation measurements.—The same dried samples used for sulfate analysis were used to measure optical rotation. Samples were weighed and dissolved in distilled water at a concentration of 5 mg/mL, and their optical rotations were determined at the sodium D-line on a Jasco model DIP-140 spectropolarimeter (Tokyo, Japan).

^{1}H NMR spectroscopy.—^{1}H NMR spectroscopy was performed under the conditions described previously [29]. Briefly, oversulfated chondroitin sulfate (approximately 2 mg) was dissolved in 0.5 mL of deuterium oxide (99.9%) and freeze-dried repeatedly to remove exchangeable protons. The sample was kept in a desiccator over phosphorus pentoxide in vacuo overnight at room temperature. The thoroughly dried sample was then dissolved in 0.5 mL of deuterium oxide (99.96%) and passed through 0.45 μm syringe filter and transferred to a NMR tube (5.0 mm o.d. × 25 cm, pp-528; Wilmad Glass, Buena, NJ). 1D and 2D NMR experiments were performed on a JEOL GSX500A spectrometer equipped with 5-mm field gradient-tunable probe with standard JEOL software at 303 K for NOE spectra or 333 K for other experiments on 500 μL samples. The HOD signal was suppressed by presaturation during 3 or 1.5 s for 1D or 2D spectra, respectively. To obtain 2D spectra, 512 experiments resulting 1024 data points for a spectral width of 2000 Hz were measured, and the time-domain data were multiplied after zerofilling (data matrix size, 1 K × 1 K) with a shifted sine-bell window functions for 2D double-quantum-filtered (DQF)-COSY, NOESY or TOCSY experiments. An MLEV-17 mixing sequence of 100 ms was used for 2D TOCSY and NOESY experiments by using 150, 250 and 500 ms as the mixing time were performed.

Anti-factor Xa and anti-factor IIa activities.—Normal human plasma (NHP) was collected from healthy volunteers. Anti-factor Xa activity was determined using a Coatest LMW heparin/heparin kit (Chromogenix, Mölndal, Sweden). Briefly, chondroitin sulfate, oversulfated chondroitin sulfate derivatives, and LMW heparin standard were in diluted normal human plasma. Chromogenic Xa substrate S-2732 (Suc-Ile-Glu(γ-Piperidyl)-Gly-Arg-*p*NA) 2.9 mM in 50 mM Tris, 7.5 μM EDTA, pH 8.4 buffer (200 μL), was added to 25 μL of plasma containing sample and 200 μL of bovine Factor Xa (1.25 mL^{-1}). After mixing, the reaction was incubated for 8 min at 37 °C and 200 μL of 20% aqueous CH_3COOH was added. Residual factor Xa was then determined by measuring absorbance at 405 nm. Anti-factor IIa activity was determined by incubating 50 μL of chondroitin sulfate or oversulfated derivatives in 30 μL of NHP with 20 μL of human thrombin (1.2 NIH units/mL) at 37 °C for 30 s. Then, 50 μL (1.9 μmol/mL) of Chromogenic TH (ethylmalonyl-Pro-Arg-*p*-nitroanilide hydrochloride) was added, and the amidolytic thrombin activity was measured at 405 nm. Measurements were performed on an ACL 300 plus from Instrumentation (Lexington, MA) and calculated in comparison with USP Heparin Reference Standard (K-3) supplied by U.S. Pharmacopeial Convention (Rockville, MD) [26].

Acknowledgements

We thank Shin Nippon Yakugyo, (Tokyo, Japan) and New Zealand Pharmaceuticals (Palmerston North, New Zealand) for supplying a chondroitin sulfate sample. This work was supported in part by Grants-in-Aid from the Ministry of Culture and Education of Japan (09672185 and 09470490) and the NIH (GM 38060 and HL 52622).

References

[1] K. Kimata, M. Okayama, A. Oohira, and S. Suzuki, *Mol. Cell. Biochem.*, 1 (1973) 211–228.

[2] J.T. Gallagher, M. Lyon, and W.P. Steward, *Biochem. J.*, 236 (1986) 313–325.

[3] M.C. Bourin, A.K. Ohlin, D. Lane, J. Stenflo, and U. Lindahl, *J. Biol. Chem.*, 263 (1988) 8044–8052.

[4] H. Engelberg, *Pharmacol. Rev.*, 36 (1984) 91–109.

[5] P. Sie, F. Ofosu, F. Fernadez, M.R. Buchanan, M. Petitou, and B. Boneu, *Br. J. Haematol.*, 64 (1986) 707–774.

[6] R.J. Linhardt, T. Toida, in Z.B. Witczak and K.A. Nieforth (Eds.), *Carbohydrates as Drugs— Heparin Oligosaccharides— New Analogs Development and Applications*, Marcel Dekker, New York, 1997, pp 277–341.

[7] B. Casu, *Adv. Carbohydr. Chem. Biochem.*, 43 (1985) 51–134.

[8] N. Razi, E. Feyzi, I. Bjork, A. Naggi, B. Casu, and U. Lindahl, *Biochem. J.*, 309 (1995) 465–472.

[9] M.C. Bourin, A. Lundgren, E. Kerlund, and U. Lindahl, *J. Biol. Chem.*, 265 (1990) 15424–5431.

[10] G. Qiu, T. Toida, and T. Imanari, *Biol. Pharm. Bull.*, 102 (1997) 721–726.

[11] B. Casu, *Semin. Thromb. Haemost.*, 17S (1991) 9–14.

[12] R.E. Edens, A. Al-Hakim, J.M. Weiler, D.G. Rethwisch, J. Fareed, and R.J. Linhardt, *J. Pharm. Sci.*, 81 (1992) 823–827.

[13] T. Toida, H. Yoshida, H. Toyoda, I. Koshiishi, T. Imanari, R.E. Hileman, J.R. Fromm, and R.J. Linhardt, *Biochem. J.*, 322 (1997) 499–506.

[14] R.J. Linhardt, in A. Varki (Ed.), *Current Protocols in Molecular Biology*, Vol. 2, Wiley Interscience, Boston, 1992, pp 17.13.17–17.13.32.

[15] F. Cabassi, B. Casu, and A.A. Perlin, *Carbohydr. Res.*, 63 (1978) 1–11.

[16] B. Casu, G. Scovenna, A.J. Cifonelli, and A.A. Perlin, *Carbohydr. Res.*, 63 (1978) 13–27.

[17] S.F.D. Orr, *Biochim. Biophys. Acta*, 14 (1954) 173–181.

[18] D. Grant, W.F. Long, C.F. Moffat, and F.B. Williamson, *Biochem. J.*, 275 (1991) 193–197.

[19] P.N. Sanderson, T.N. Huckerby, I. Nieduszynski, and A. Nieduszynski, *Biochem. J.*, 243 (1987) 175–181.

[20] R.M. Maaroufi, J. Tapon-Bretandiere, J. Mardiguian, C. Sternberg, M.D. Dauztenberg, and A.M. Fischer, *Thromb. Res.*, 59 (1995) 174–758.

[21] C. Bartolucci, L. Cellai, M.A. Iannelli, D. Lamba, L. Liverani, G. Mascellani, and E. Perola, *Carbohydr. Res.*, 276 (1995) 401–408.

[22] R.J. Linhardt, A. Al-Hakim, L.S. Yu, Y.S. Kim, and J. Fareed, *Semin. Thromb. Haemost.*, 17S (1991) 15–22.

[23] R.J. Linhardt, A. Al-Hakim, J. Lin, D. Hoppensteadt, G. Mascellani, P. Bianchini, and J. Fareed, *Biochem. Pharmacol.*, 42 (1991) 1609–1691.

[24] Y.S. Kim and R.J. Linhardt, *Thromb. Res.*, 53 (1989) 57–71.

[25] R.J. Linhardt and R.E. Hileman, *Gen. Pharmacol.*, 26 (1995) 443–451.

[26] V.D. Nadkarni, T. Toida, C.L. van Gorp, R.L. Schubert, J.M. Weiler, K.P. Hansen, E.E.O. Caldwell, and R.J. Linhardt, *Carbohydr. Res.*, 290 (1996) 87–96.

[27] K. Nagasawa, H. Uchiyama, and N. Wajima, *Carbohydr. Res.*, 158 (1986) 183–190.

[28] H. Toyoda, H. Motoki, M. Tanikawa, K. Shinomiya, H. Akiyama, and T. Imanari, *J. Chromatogr.*, 565 (1991) 141–148.

[29] T. Toida, H. Toyoda, and T. Imanari, *Anal. Sci.*, 9 (1993) 53–58.

nature
biotechnology

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events

Marco Guerrini[1,7], Daniela Beccati[2,7], Zachary Shriver[2,3,7], Annamaria Naggi[1], Karthik Viswanathan[3], Antonella Bisio[1], Ishan Capila[2], Jonathan C Lansing[2], Sara Guglieri[1], Blair Fraser[4], Ali Al-Hakim[4], Nur Sibel Gunay[2], Zhenqing Zhang[5], Luke Robinson[3], Lucinda Buhse[4], Moheb Nasr[4], Janet Woodcock[4], Robert Langer[3,6], Ganesh Venkataraman[2,3], Robert J Linhardt[5], Benito Casu[1], Giangiacomo Torri[1] & Ram Sasisekharan[3]

Recently, certain lots of heparin have been associated with an acute, rapid onset of serious side effects indicative of an allergic-type reaction. To identify potential causes for this sudden rise in side effects, we examined lots of heparin that correlated with adverse events using orthogonal high-resolution analytical techniques. Through detailed structural analysis, the contaminant was found to contain a disaccharide repeat unit of glucuronic acid linked β1→3 to a β-*N*-acetylgalactosamine. The disaccharide unit has an unusual sulfation pattern and is sulfated at the 2-*O* and 3-*O* positions of the glucuronic acid as well as at the 4-*O* and 6-*O* positions of the galactosamine. Given the nature of this contaminant, traditional screening tests cannot differentiate between affected and unaffected lots. Our analysis suggests effective screening methods that can be used to determine whether or not heparin lots contain the contaminant reported here.

Heparin, a complex glycosaminoglycan polysaccharide, is widely used as an anticoagulant in a number of settings, including kidney dialysis and acute coronary syndromes[1–3]. The most serious adverse event associated with heparin, aside from a potential bleeding risk, is thrombocytopenia. Recently there has been a marked increase in serious adverse events associated with heparin therapy, with hundreds of individuals affected[4–7]. Although heparin therapy is generally well tolerated, recently patients presented—within several minutes after intravenous infusion of unfractionated heparin—with angioedema, hypotension, swelling of the larynx and related symptoms, which in some cases ended in death. Because heparin is a drug commonly used in the clinic, occurrence of these adverse events resulted in a crisis in the United States. Germany and other nations in the European Union have observed similar phenomena, turning this health problem into an international issue[4,5]. The rapid onset of these symptoms suggests an anaphylactic response, but the exact etiology is currently unknown. Given the clinical history of heparin, this spike in adverse events suggests the potential contamination of heparin. However, standard testing of heparin lots for typical biological contaminants, including protein, lipids and DNA (which, if present, may elicit such side effects), indicated that there is no difference in these regards between lots that elicit adverse events and those that do not[4]. Despite extensive analysis, no obvious differences were found with respect to other potential contaminants, including lead, dioxins and other molecular entities[8]. Definitive identification of how these heparin lots differ from the clinically approved heparin thus becomes imperative[9].

To understand the structure or structures of the contaminant(s) present within specific lots of heparin, we sought to identify these contaminants. This exercise required the use of multiple orthogonal techniques, including multidimensional NMR, to overcome the challenges inherent in the analysis of complex polysaccharides, including heparin, which in and of itself comprises a complex mixture of glycosaminoglycan chains. In doing so, we were able to determine definitively the structure of the contaminant, isolate it and confirm its structural identity by comparison to a chemically synthesized standard.

RESULTS

NMR shows unusual *N*-acetyl signals not seen in heparin

For this study, we examined lots that were associated with adverse clinical reactions (designated S1–S6) as well as four control lots of heparin not associated with adverse events (designated C1–C4). Initial analysis of S1–S6 by one-dimensional NMR indicated that all of these samples produced an unusual series of *N*-acetyl signals (**Fig. 1a, Supplementary Figs. 1** and **2** online). For example, particularly evident in the proton spectrum of S1 is the signal at 2.16 p.p.m. corresponding to an *N*-acetyl group different from that of heparin (2.04 p.p.m.). This *N*-acetyl signal is also distinct from that of

---

[1]Istituto di Ricerche Chimiche e Biochimiche "G. Ronzoni," Città Studi, via Giuseppe, Colombo 81, 20133 Milan, Italy. [2]Momenta Pharmaceuticals, Inc., 675 West Kendall Street, Cambridge, Massachusetts 02142, USA. [3]Department of Biological Engineering, Harvard-MIT Division of Health Sciences & Technology, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, Massachusetts 02139, USA. [4]Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, Maryland 20993-0002, USA. [5]Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, Troy, New York 12180, USA. [6]Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, Massachusetts 02139, USA. [7]These authors contributed equally to this work. Correspondence should be addressed to R.S. (rams@mit.edu).

Received 21 March; accepted 18 April; published online 23 April 2008; doi:10.1038/nbt1407

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

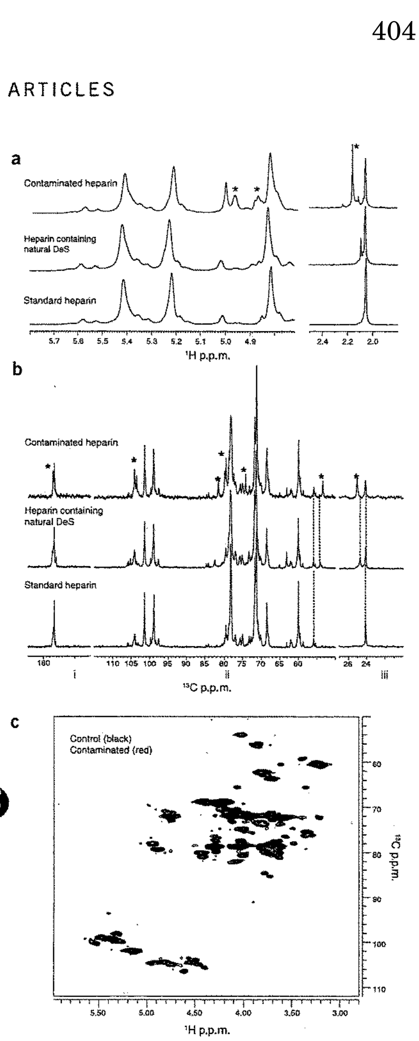


Figure 1 NMR analysis of contaminated heparin. (**a**) Comparison of anomeric and acetyl regions of the proton spectra of standard heparin, heparin containing natural dermatan sulfate (DeS) and contaminated heparin. (**b**) Comparison of carbonyl (i), sugar (ii) and *N*-acetyl regions (iii) of the carbon spectra of standard heparin, heparin containing natural dermatan sulfate, and contaminated heparin. Signals due to the contaminant are highlighted by asterisks. (**c**) HSQC spectrum of the contaminated sample S1 overlaid on control sample C1.

dermatan sulfate, a known impurity in heparin samples (2.08 p.p.m)[10]. To complement and extend the proton analysis, carbon (100 MHz) NMR spectroscopy was performed. Comparison of the carbon spectra of S1 and C1 indicates the presence of several additional signals not normally associated with heparin structural signatures (**Fig. 1b**). The acetyl signal at 25.6 p.p.m together with the signal at 53.5 p.p.m are indicative of the presence of an *O*-substituted *N*-acetylgalactosamine residue of unknown structure, but again distinct from the *N*-acetylgalactosamine contained within dermatan sulfate, with corresponding signals at 24.8 p.p.m and 54.1 p.p.m, respectively. Other signals are visible in the ring and anomeric regions of the carbohydrate moiety. The latter signals (103–105 p.p.m) agree with a beta configuration of glycosidic linkages for the contaminant.

To further identify the number and type of any major contaminants, we collected multidimensional heteronuclear single quantum coherence (HSQC) spectra on S1 and C1 to separate the observed signals in two dimensions—the carbon and proton signals. Ten major signals observed in sample S1 were not seen in C1. These same signals were observed in samples S2–S6 but not in samples C2–C4 (**Supplementary Figs. 3 and 4 online**). In addition, these results and those from other two-dimensional experiments, including total correlation spectroscopy (TOCSY), correlation spectroscopy (COSY) and rotating-frame nuclear Overhauser effect spectroscopy (ROSEY), were also consistent with the basic findings outlined above, namely that the principal contaminant consists of a polymeric repeat of *N*-acetylgalactosamine linked to glucuronic acid exclusively through beta linkages.

Identification of an impurity and a contaminant in heparin

Much of the analysis outlined above focused on sample S1, as it possessed signals in the *N*-acetyl region at 2.04 p.p.m (arising from heparin) and at 2.16 (arising from the unknown contaminant). In addition to this unusual signal at ~2.16 p.p.m, some samples (S2–S6 and C2–C4) possessed an additional *N*-acetyl peak (**Supplementary Fig. 5b online**), which had a chemical shift of 2.08 p.p.m, indicating the presence of another species that is distinct from the contaminant. Given the observed chemical shifts, this species is most likely dermatan sulfate, a known natural impurity of heparin[10,11]. To confirm the identity of this species, we performed a two-dimensional (2D) ^{1}H-^{13}C HSQC experiment on C2 (**Supplementary Fig. 5d**) and compared the results to those obtained on C1, a sample that did not show this additional signal. The chemical shifts observed in C2 but not in C1 are similar to those reported in the literature[10], and this observation suggests that the additional peaks in the HSQC of C2 can be assigned to dermatan sulfate. This assignment was confirmed by comparison to ^{1}H and HSQC data obtained on a standard of dermatan sulfate (**Supplementary Fig. 5a,c**). Through an analysis similar to that completed on sample C2, we confirmed the presence of dermatan sulfate in those samples presenting a proton NMR signal at 2.08 p.p.m. Therefore, samples S2–S6, but not sample S1, contained both dermatan sulfate (an impurity typically found in heparin) and the unusual contaminant.

Finally, to confirm the findings from the NMR analysis of the samples, we conducted enzymatic digestion of S1–S6 and C1–C4 with either a combination of heparinases or heparinases plus Δ4,5 glycuronidase and 2-O sulfatase followed by separation and analysis by high-performance liquid chromatography (HPLC). Digestion with the heparinases reduces heparin to its component di-, tri- and tetrasaccharides and imparts a Δ4,5 bond that can be monitored at 232 nm; completed in conjunction with treatment with glycuronidase and sulfatase, this digest permits the identification of minor heparin

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

species, including those disaccharides containing a modified galacturonic acid[12,13]. Thus, concomitant use of a matrix of enzymes, especially in conjunction with liquid chromatography–tandem mass spectrometry analysis, allows for the complete separation, identification and quantification of heparin components in the mixture[14]. We find that the total areas under the curve, calculated by integration of all heparin di-, tri- and tetrasaccharides observed in the HPLC and summation of the resulting areas, of digested S1–S6 are substantially less than those of the control samples, indicating that the major contaminant is not substantially digested by the heparinases (**Table 1**). Furthermore, the difference in the area under the curve is correlated with the amount of contaminant present within the sample; samples with larger amounts of contaminant (as measured by proton NMR) had a lower area under the curve as measured by HPLC. Finally, the relative quantities of the individual heparin components are similar between the controls and suspect samples, with only minor differences.

To identify the unknown compound present in the contaminated heparin samples, we attempted to isolate the contaminant using a variety of methods. Given the overall properties of the contaminant, elucidated through NMR, capillary electrophoresis and HPLC analysis, we reasoned that this material could be differentially precipitated upon addition of an organic solvent. Partial purification of the contaminant was indeed achieved through the addition of increasing amounts of ethanol to an aqueous solution of S1. Similarly, because the contaminant contains *N*-acetylhexosamine (and not *N*-sulfohexosamine), it was also purified by degradation of heparin by nitrous acid and isolation of the remaining components.

Isolation of the contaminant allowed definitive identification

After isolation, the proton spectrum of the isolated contaminant reveals a residual heparin content of ~10–30% (depending on the isolation method used) as determined by one-dimensional NMR (data not shown). We carried out additional, detailed NMR studies on this isolated sample. To facilitate an understanding of the experiments and their interpretation, the disaccharide repeat structures of heparin, chondroitin sulfate, dermatan sulfate and heparin, together with positional nomenclature, are presented in **Figure 2**. In the carbon spectrum, at neutral pH values, one apparent signal arises at 177.6 p.p.m, characteristic of carbonyl groups. Acidification of a solution of the product from pH 6.5 to pH 4 (**Fig. 3a**) reveals two distinct carbonyl signals consistent with the carbonyl group of an *N*-acetyl function and the protonated form of carboxylic acid, respectively. Similar shifts were not observed for any other signals except C-5 of uronic acid (U5), for which this carbon's chemical shift is sensitive to the ionization state of the carboxylic acid as well as the identity of the counterion present (**Fig. 3b**). To further characterize the isolated sample, we used homonuclear (COSY and TOCSY, data not shown) and heteronuclear (HSQC, HSQC-TOCSY and heteronuclear multiple bond correlation (HMBC)) 2D-NMR spectroscopy (**Fig. 3c,d**). These analyses indicated the presence of two types of residues. Chemical shift patterns were in agreement with one type of monosaccharide being a 4,6-*O*-sulfo-*N*-acetylgalactosamine and the other being a 2,3-*O*-sulfoglucuronic acid. In addition to confirming the assignments of the sugar moieties, the HMBC spectrum demonstrated the correlation across the glycosidic linkages, indicating the presence of a β-1,4 linkage between galactosamine and glucuronic acid and a β-1,3 linkage between the glucuronic acid and the galactosamine. Confirmatory evidence of this structure was provided by the long-range correlations of H1 of the galactosamine and H5 of glucuronic acid with two different carbonyl groups (177.5 and 177.8 p.p.m) owing to the *N*-acetyl of galactosamine and the carboxylic group of glucuronic acid.

Synthetic oversulfated chondroitin matches contaminant

The identification of the contaminant as an oversulfated chondroitin sulfate containing a tetrasulfated disaccharide unit consisting of glucuronic acid linked to *N*-acetylgalactosamine was surprising, as this is an unusual structure. To ensure the accuracy of this assignment, we prepared a standard by oversulfation of chondroitin sulfate using well-established chemistry. We analyzed this

Table 1 Total area under the curve for heparinase digests of S1–S6 and C1–C4

Sample	Total area
C1	2.52×10^7
C2	2.70×10^7
C3	2.33×10^7
C4	2.39×10^7
S1	1.74×10^7
S2	9.50×10^6
S3	1.94×10^7
S4	1.59×10^7
S5	1.91×10^7
S6	1.96×10^7

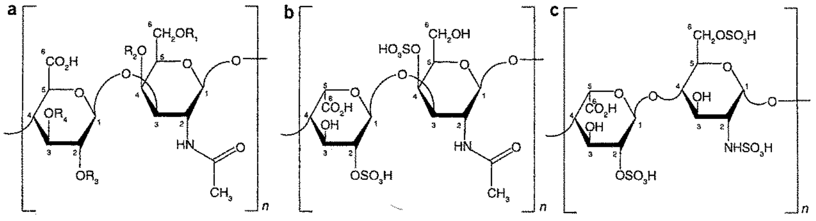


Figure 2 Chemical structures of major repeat units. (**a–c**) Schematic of major disaccharide repeat units of chondroitin sulfate (**a**), dermatan sulfate (**b**) and heparin (**c**). The carbon atoms are numbered for each monosaccharide of the disaccharide repeat. For chondroitin sulfate, R1-R4 can be either sulfated or unsubstituted.

standard by 2D NMR and carefully compared the HSQC spectra to both the literature[15] and the HSQC spectrum obtained for the isolated contaminant. Comparison of the HSQC spectrum of the synthesized standard with that of the isolated contaminant (**Fig. 4**) confirmed that the major contaminant consists of per-O-sulfated chondroitin sulfate, with all of the hydroxyl groups of both the uronic acid and galactosamine residues bearing sulfate substituents. Furthermore, the proton chemical shifts of the contaminant (**Table 2**) are in agreement with those assigned to fully sulfated chondroitin (degree of sulfation = 4)[15]. In addition, mass spectrometry completed after enzymatic digestion of a chemically desulfated[16] version of the contaminant was consistent with the proposed structure (**Fig. 5**). The final derived structure of the major contaminant present in heparin is shown in **Figure 2a**, with R_1, R_2, R_3 and R_4 all sulfated.

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

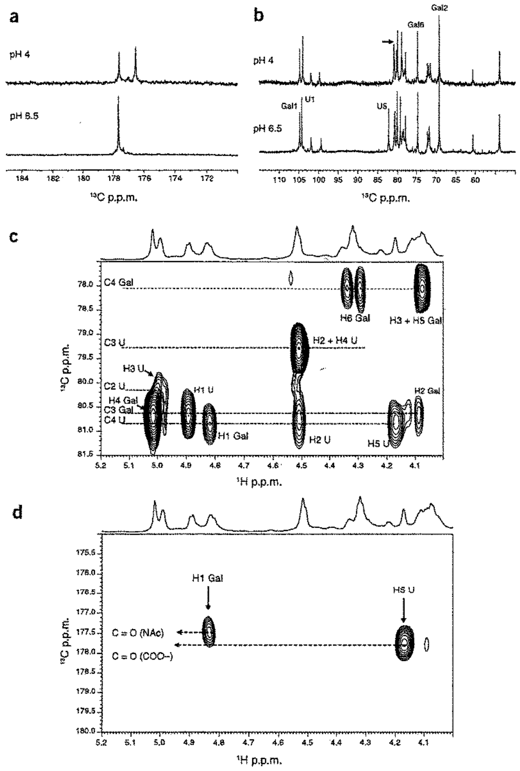


Figure 3 Detailed NMR structural analysis of the contaminant. (**a**) Carbonyl region of the carbon spectrum of the contaminant measured at pH 6.5 and 4. (**b**) Sugar region of the carbon spectrum of the contaminant measured at pH 6.5 and 4. The arrow points to the shift in the C5 of glucuronic acid (U5) upon pH adjustment. (**c**) A portion of the 600-MHz HMBC spectrum of the contaminant. Intramolecular two- and three-bond proton-carbon correlations are shown in black; interglycosidic proton-carbon correlations are indicated in blue; carbon connectivity shown in red. (**d**) Portion of the 600-MHz HMBC spectrum of the contaminant. Long-range correlation between the H1 of *N*-acetylgalactosamine (Gal) with the C=O of the acetyl group and H5 of glucuronic acid (U) with the carboxylic group are shown.

DISCUSSION

Several factors required the use of multiple approaches to ensure an accurate structural determination of the oversulfated chondroitin contaminant. First, heparin is a chemically complex polydisperse mixture of saccharides, making careful interpretation of results necessary to avoid misinterpretation. Detailed analysis is especially important when addressing the multiple isomeric possibilities within the chains of a complex mixture, and it necessitates the use of orthogonal techniques, including an enzyme matrix and multidimensional NMR. Second, oversulfated materials, such as the chondroitins, are resistant to enzymatic digestion techniques and copurify with heparin, rendering their isolation challenging[15,17].

These complexities manifest themselves in a number of ways: for example, structurally distinct species may have overlapping signals and properties, thereby 'masking' them within a single analysis. A nonintegrated approach can therefore potentially lead to false conclusions, especially when attempting to differentiate between heparin, dermatan sulfate and oversulfated chondroitin sulfate in any given sample. In this study, we present a set of experimental techniques that discriminate between dermatan sulfate (a known impurity of heparin) and oversulfated chondroitin sulfate.

The structure of the contaminant, which contains a tetrasulfated disaccharide repeat, is highly unusual. First, the presence of a 3-O-sulfated glucuronic acid is rare, only observed in specific contexts within certain organisms[18]. In addition, a tetrasulfated disaccharide repeat unit has not been isolated to date from animal tissues. Consequently, it is highly unlikely that the contaminant reported here is produced naturally. Finally, chemically synthesized tetrasulfated disaccharide repeat units of chondroitin sulfate are known to exhibit a high degree of anti–factor IIa activity[15], which could explain how contaminated heparin would pass an activity screen, such as a whole-blood coagulation test. Further investigation is warranted to understand how this contaminant was introduced.

With respect to the potential biological ramifications of this finding, it is possible that the presence of an oversulfated chondroitin sulfate within heparin preparations

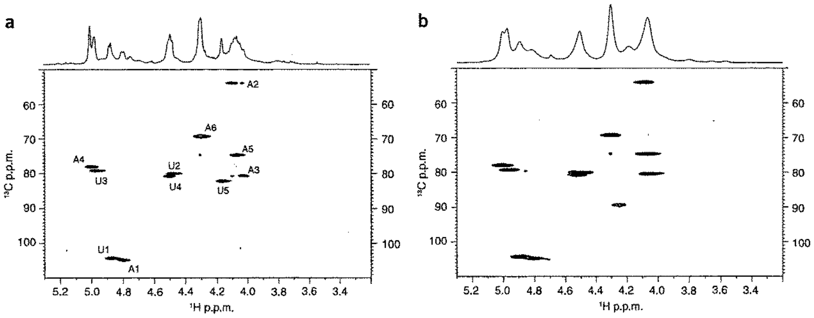


Figure 4 Structural assignment of the contaminant by NMR using isolated and synthetic materials. **(a)** ^{1}H-NMR and HSQC spectra of the isolated contaminant. Signals for 4,6-*O*-sulfo-*N*-acetylgalactosamine (A) and of 2,3-*O*-sulfo-glucuronic acid (U) are labeled. **(b)** ^{1}H-NMR and HSQC spectra of the chemically synthesized oversulfated chondroitin.

© 2008 Nature Publishing Group http://www.naturebiotechnology

can provoke increased side effects. In the case of chondroitins, chondroitin sulfates A and C are expressed by human cells and are generally nonimmunogenic. Highly sulfated polysaccharides, however, such as oversulfated chondroitins, have been shown to be potent mediators of the immune response[19–22]. Indeed, complications associated with administration of highly sulfated chondroitins have been observed in humans. Arteparon, an oversulfated chondroitin that is structurally identical to the contaminant[23] (**Fig. 2**), injected intramuscularly in humans[24], was marketed for the treatment of degenerative joint disease in Europe. It was demonstrated that this product can induce an allergic-type response[25]. Because of patient deaths, most likely due to thromboembolic complications, the product was rapidly withdrawn from the European market[26]. The structural determination of the contaminant described here enables further investigation into the biological roles and potential pharmacological effects of oversulfated chondroitins, present within heparin preparations, in the recently reported adverse events.

Taken together, our orthogonal analytical experiments provide strong support for the structure we have assigned to the contaminant. This study also provides a set of screening methods that could be used to monitor the heparin supply and ensure the absence of oversulfated chondroitin sulfate contamination. For example, using the structural information presented here, it is now possible to (i) design reference standards that ensure accuracy, quantification and specificity of analysis for a given analytical method and (ii) devise an experimental protocol to clearly define the nature and extent, if any,

Table 2 Chemical shifts observed for contaminant by two independent laboratories and comparison to literature data on oversulfated chondroitin sulfate

Monosaccharide	Lab 1[a]		Lab 2[b]		^{1}H (literature)[c], fully *O*-sulfonated CS
	^{1}H (observed)	^{13}C (observed)	^{1}H (observed)	^{13}C (observed)	
4,6-*O*-Sulfo-*N*-acetyl-galactosamine					
H1/C1	4.77	105.0	4.79	104.8	4.86
H2/C2	4.06	54.0	4.10	54.0	4.10
H3/C3	4.05	80.7	4.03	80.7	4.10
H4/C4	4.98	78.0	5.00	78.0	5.02
H5/C5	4.05	74.8	4.07	74.7	4.06
H6,6′/C6	4.28	69.3	4.30	69.2	4.29
N-Acetyl	2.12[d]	25.6	2.16[e]	25.6	2.16
2,3-*O*-Sulfo-glucuronic acid					
H1/C1	4.87	104.5	4.87	104.3	4.97
H2/C2	4.47	80.0	4.49	80.0	4.53
H3/C3	4.95	79.3	4.98	79.2	4.94
H4/C4	4.46	80.9	4.51	80.8	4.55
H5/C5	4.12	82.0	4.17	82.2	4.20

[a]Chemical shifts are measured at 303 K and referenced to external 2,2-dimethyl-2-silapentane-5-sulfonate sodium salt (DSS). [b]Chemical shifts are measured at 308 K and referenced to external sodium trimethylsilylpropionate (TSP) (which resonates 0.12 p.p.m upfield of DSS[29]). [c]Measured at 303 K and referenced to TSP (ref. 15). CS, chondroitin sulfate. [d]Additional minor signals observed at 2.20 and 2.07 p.p.m. [e]Additional minor signals observed at 2.23 and 2.11 p.p.m.

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

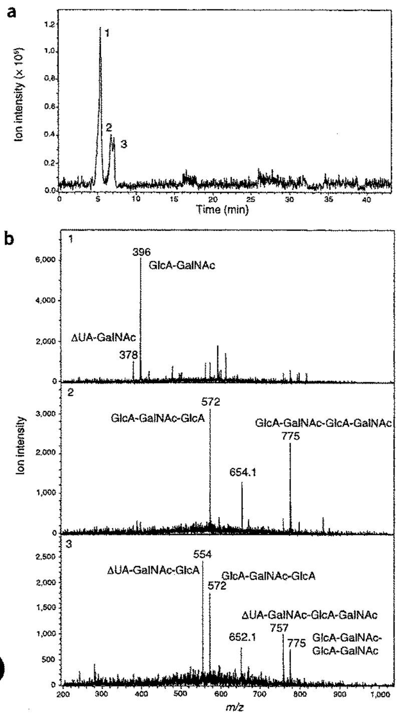


Figure 5 Liquid chromatography–mass spectrometry (LC-MS) analysis of the contaminant. (**a**) Total ion chromatogram with detection of three peaks (1–3). (**b**) Specific ions and associated structures observed in each peak. After desulfation, the contaminant was digested with chondroitinase ABC and analyzed by LC-MS. The presence of saturated and unsaturated oligosaccharides indicates that the backbone of the impurity could be digested with chondroitinase ABC and suggests that the backbone is a glucuronic acid–*N*-acetylgalactosamine repeat (UA-GalNAc).

of contamination in a given lot of heparin. Finally, the ramifications of these findings extend beyond scientific considerations and include clinical and health policy issues.

METHODS

Materials. Chondroitin sulfate type A from whale cartilage, pyridine–sulfur trioxide complex, tributylamine, dry *N,N*-dimethylformamide, pyridine, methanol, dimethylsulfoxide, $NaNO_2$, $NaBH_4$, 2,2-dimethyl-2-silapentane-5-sulfonate sodium salt and sodium trimethylsilylpropionate were purchased from Sigma-Aldrich. Tetrabutylammonium chloride was purchased from Fluka. 99.9% D_2O and 99.96% D_2O were obtained from Cambridge Isotope laboratories. The following ten lots of unfractionated heparin were tested: S1, S2, S3, S4, S5, S6, C1, C2, C3 and C4. All heparin samples were supplied by the FDA.

NMR analysis. Samples for ^{1}H-NMR or 2D NMR analysis were dissolved in 0.7 ml of D_2O (99.9%) and were either freeze-dried repeatedly to remove exchangeable protons or directly measured without any treatment to preserve potential volatile components. The thoroughly dried samples were dissolved in 0.7 ml of D_2O (99.96%). Before spectrum acquisition, samples were sonicated for 60 s to remove air bubbles. Spectra were obtained at 303 K or 308 K using a 600-MHz Varian VNMRS spectrometer or a 600-MHz Bruker Avance 600 spectrometer, both equipped with a 5-mm triple-resonance inverse cryoprobe. Monodimensional ^{1}H spectra were obtained with presaturation of residual HOD, for 32–128 scans. DQF-COSY and 2D-TOCSY spectra were acquired using 32 scans per series of 2,048 × 512 data points. HSQC and HSQC-TOCSY spectra were recorded with carbon decoupling during acquisition with 320 increments for 12–64 scans. The polarization transfer delay was set with a $^1J_{C\text{-}H}$ coupling value of 155 Hz. HMBC spectrum was recorded with 320 increments of 64 scans for each, without carbon decoupling and with twofold low-pass J-filter to suppress one-bond correlations[27]. The delay for evolution of long-range couplings was set with a J_{lr} of 8 Hz. Samples for ^{13}C-NMR analysis were dissolved in D_2O (99.9%) at 40 mg/ml and analysis was performed at 303 K with a 400-MHz Bruker spectrometer equipped with a multinuclear probe.

Composition analysis by ion-pair RPHPLC. Samples were constituted in capillary electrophoresis–grade water and digested under two different conditions. The first digest used an enzyme cocktail of heparinases I (500 mIU), II (400 mIU) and III (500 mIU) at 30 °C, for 16 h. A portion of this digest was further treated with 2-*O*-sulfatase (1,000 mIU) and Δ4,5-glycuronidase (2,000 mIU) for 6 h at 30 °C to obtain the second digest. Each digest was passed through a Ni^{2+} spin column (Qiagen) and analyzed by ion-pair RPHPLC similar to as previously described[14]. Elution was monitored by UV detection at 232 nm.

Isolation of major contaminant. Absolute ethanol was added to sample S1 (300 mg), dissolved in 1.5 ml of water until a white precipitate appeared (ethanol 23%, vol/vol). Precipitated material was separated by centrifugation for 5 min at 5,000 r.p.m. (~4,000g) on a Labofuge 200 (Heraeus). In addition to the above, sample S1 was treated with nitrous acid[28]. A solution of the sample (500 mg) was dissolved in 20 ml of H_2O and cooled at 4 °C. Also at 4 °C, 140 mg of $NaNO_2$ dissolved in 1 ml of water was added to the sample and the pH was adjusted to 1.7 with 0.1 M HCl. The solution was stirred at 4 °C for 20 min; an additional 100 mg $NaNO_2$ was added and the solution stirred for another 20 min. The solution pH was then adjusted to 7 with NaOH and the resulting reaction was brought to room temperature. Solid $NaBH_4$ (200 mg) was added in several portions with stirring. After 2 h, the pH was adjusted to 4 with 0.1 M HCl and the solution was neutralized with 0.1 M NaOH. The product, obtained by precipitation with four volumes of methanol, was recovered by centrifugation, dissolved in water and freeze-dried.

Chemical sulfonation of chondroitin sulfate. Fully sulfated chondroitin sulfate was prepared from chondroitin sulfate, as described[15]. Chondroitin sulfate (108 mg) was converted into its tributylamine salt and dissolved in dry *N,N*-dimethylformamide (1 ml). After addition of 159 mg of pyridine–sulfur trioxide complex, the solution was heated for 1 h at 40 °C . The reaction was interrupted by addition of 2 ml of water and the product was precipitated at 4 °C by addition of 35 ml of an ethanol solution saturated with sodium acetate. The product recovered by centrifugation was dissolved in water, dialyzed at room temperature and recovered by freeze-drying.

Note: Supplementary information is available on the Nature Biotechnology website.

ACKNOWLEDGMENTS
The authors would like to thank Sucharita Roy for work on the chemical synthesis of oversulfated chondroitin sulfate standards, Scott Bailey for assistance in the analysis of selected samples by one- and two-dimensional NMR and Laura Citterio for work in various separation and analytical steps. We also thank James Anderson, Josh Sorafine and Andre Jones for design of composition experiments and HPLC analysis of the heparinase-digested samples. Finally, we thank Ada Ziolkowski for help with manuscript preparation. This work was supported in

part by US National Institute of General Medical Sciences grants GM57073 (R.S.) and GM38060 (R.J.L).

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

Published online at http://www.nature.com/naturebiotechnology/
Reprints and permissions information is available online at http://npg.nature.com/reprintsandpermissions/

1. Capila, I. & Linhardt, R.J. Heparin-protein interactions. *Angew. Chem. Int. Edn. Engl.* **41**, 391–412 (2002).
2. Lepor, N.E. Anticoagulation for acute coronary syndromes: from heparin to direct thrombin inhibitors. *Rev. Cardiovasc. Med.* **8** (suppl. 3), S9–S17 (2007).
3. Fischer, K.G. Essentials of anticoagulation in hemodialysis. *Hemodial. Int.* **11**, 178–189 (2007).
4. Contaminant detected in heparin material of specified origin in the USA and in Germany; serious adverse events reported; recall measures initiated. World Health Organization Alert No. 118 (7 March 2008). <http://www.who.int/medicines/publications/drugalerts/Alert_118_Heparin.pdf>
5. Notice of Recall from Rotexmedica to Bfarm (German Regulatory Authorities). Rotexmedica/Bfarm Notice (7 March 2008). <http://www.akdae.de/20/40/Archiv/2008/20080310.pdf>
6. Acute allergic-type reactions among patients undergoing hemodialysis—multiple states, 2007–2008. *Morbid. Mortal. Wkly Rept.* **57** (1 February 2008).
7. 2008 Heparin Recall Information. Baxter Investigation Updates (5,14,19 March 2008). <http://www.baxter.com/products/biopharmaceuticals/heparin.html>
8. Baxter provides update on investigation. Baxter Investigation Update (14 March 2008). <http://www.baxter.com/products/biopharmaceuticals/downloads/heparin_03-14-08.pdf>
9. Communication. Information on heparin sodium injection. US Food and Drug Administration. <http://www.fda.gov/cder/drug/infopage/heparin/default.htm>
10. Holme, K.R. & Perlin, A.S. Nuclear magnetic resonance spectra of heparin in admixture with dermatan sulfate and other glycosaminoglycans. 2-D spectra of the chondroitin sulfates. *Carbohydr. Res.* **186**, 301–312 (1989).
11. Guerrini, M., Bisio, A. & Torri, G. Combined quantitative ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy for characterization of heparin preparations. *Semin. Thromb. Hemost.* **27**, 473–482 (2001).
12. Myette, J.R. *et al.* Molecular cloning of the heparin/heparan sulfate delta 4,5 unsaturated glycuronidase from *Flavobacterium heparinum*, its recombinant expression in *Escherichia coli*, and biochemical determination of its unique substrate specificity. *Biochemistry* **41**, 7424–7434 (2002).
13. Myette, J.R. *et al.* The heparin/heparan sulfate 2-*O*-sulfatase from *Flavobacterium heparinum*. Molecular cloning, recombinant expression, and biochemical characterization. *J. Biol. Chem.* **278**, 12157–12166 (2003).
14. Kuberan, B. *et al.* Analysis of heparan sulfate oligosaccharides with ion pair-reverse phase capillary high performance liquid chromatography-microelectrospray ionization time-of-flight mass spectrometry. *J. Am. Chem. Soc.* **124**, 8707–8718 (2002).
15. Maruyama, T., Toida, T., Imanari, T., Yu, G. & Linhardt, R.J. Conformational changes and anticoagulant activity of chondroitin sulfate following its *O*-sulfonation. *Carbohydr. Res.* **306**, 35–43 (1998).
16. Solvolytic desulfation of glycosaminoglycuronan sulfates with dimethyl sulfoxide containing water or methanol. Nagasawa, K., Inoue, Y. & Kamata, T. *Carbohydr. Res.* **58**, 47–55 (1977).
17. Linhardt, R.J. Analysis of glycosaminoglycans with polysaccharide lyases. in *Current Protocols in Molecular Biology* (eds. Ausubel, F.A. *et al.*) 17.13B.1–17B.13.16 (Wiley, New York, 1994).
18. Kinoshita, A. *et al.* Novel tetrasaccharides isolated from squid cartilage chondroitin sulfate E contain unusual sulfated disaccharide units GlcA(3-*O*-sulfate)β1-3GalNAc(6-*O*-sulfate) or GlcA(3-O-sulfate)β1-3GalNAc. *J. Biol. Chem.* **272**, 19656–19665 (1997).
19. Hadding, U. *et al.* Ability of the T cell-replacing polyanion dextran sulfate to trigger the alternate pathway of complement activation. *Eur. J. Immunol.* **3**, 527–529 (1973).
20. Kang, O.H. *et al.* Suppressive effect of non-anaphylactogenic anti-IgE antibody on the development of dextran sulfate sodium-induced colitis. *Int. J. Mol. Med.* **18**, 893–899 (2006).
21. Siebeck, M. *et al.* Dextran sulfate activates contact system and mediates arterial hypotension via B2 kinin receptors. *J. Appl. Physiol.* **77**, 2675–2680 (1994).
22. Hojima, Y., Cochrane, C.G., Wiggins, H.C., Austen, K.F. & Steven, R.L. In vitro activation of the contact (Hageman factor) system of plasma by heparin and chondroitin sulfate E. *Blood* **63**, 1453–1459 (1984).
23. Naggi, A. *et al.* Sulfamino-galactosaminoglycans, a new class of semi-synthetic polysaccharides. in *Biomedical and Biotechnological Advances in Industrial Polysaccharides* (eds. Crescenzi, V., Dea, I.C.M. & Paoletti, S.) 101–108 (Gordon & Breach Science, New York, 1989).
24. Siegmenth, W. & Radi, I. Comparison of glycosaminoglycan polysulfate (Arteparon) and physiological saline solution in arthrosis of the large joints. Results of a multicenter double-blind study. *Z. Rheumatol.* **42**, 223–228 (1983).
25. Greinacher, A., Michels, I., Schäfer, M., Kiefel, V. & Mueller-Eckhardt, C. Heparin-associated thrombocytopenia in a patient treated with polysulphated chondroitin sulphate: evidence for immunological crossreactivity between heparin and polysulphated glycosaminoglycan. *Br. J. Haematol.* **81**, 252–254 (1992).
26. Weimann, G. *et al.* Glucosamine sulfate does not crossreact with the antibodies of patients with heparin-induced thrombocytopenia. *Eur. J. Haematol.* **66**, 195–199 (2001).
27. Cicero, O., Barbato, G. & Bazzo, R. Sensitivity enhancement of a two-dimensional experiment for the measurement of heteronuclear long-range coupling constants, by a new scheme of coherence selection by gradients. *J. Magn. Reson.* **148**, 209–213 (2001).
28. Cifonelli, J.C. Reaction of heparitin sulfate with nitrous acid. *Carbohydr. Res.* **8**, 233–242 (1968).
29. Wishart, D.S. *et al.* ^{1}H, ^{13}C and ^{15}N chemical shift referencing in biomolecular NMR. *J. Biomol. NMR* **6**, 135–140 (1995).

© 2008 Nature Publishing Group http://www.nature.com/naturebiotechnology

The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Published at www.nejm.org April 23, 2008 (10.1056/NEJMoa0803200)

Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Takashi Kei Kishimoto, Ph.D., Karthik Viswanathan, Ph.D., Tanmoy Ganguly, Ph.D., Subbiah Elankumaran, Ph.D., Sean Smith, B.S., Kevin Pelzer, Ph.D., Jonathan C. Lansing, Ph.D., Nammalwar Sriranganathan, Ph.D., Ganlin Zhao, M.D., Zoya Galcheva-Gargova, Ph.D., Ali Al-Hakim, Ph.D., Gregory Scott Bailey, B.S., Blair Fraser, Ph.D., Sucharita Roy, Ph.D., Thomas Rogers-Cotrone, M.S., Lucinda Buhse, Ph.D., Mark Whary, Ph.D., James Fox, Ph.D., Moheb Nasr, Ph.D., Gerald J. Dal Pan, M.D., Zachary Shriver, Ph.D., Robert S. Langer, Sc.D., Ganesh Venkataraman, Ph.D., K. Frank Austen, M.D., Janet Woodcock, M.D., and Ram Sasisekharan, Ph.D.

ABSTRACT

Background There is an urgent need to determine whether oversulfated chondroitin sulfate (OSCS), a compound contaminating heparin supplies worldwide, is the cause of the severe anaphylactoid reactions that have occurred after intravenous heparin administration in the United States and Germany.

Methods Heparin procured from the Food and Drug Administration, consisting of suspect lots of heparin associated with the clinical events as well as control lots of heparin, were screened in a blinded fashion both for the presence of OSCS and for any biologic activity that could potentially link the contaminant to the observed clinical adverse events. In vitro assays for the activation of the contact system and the complement cascade were performed. In addition, the ability of OSCS to recapitulate key clinical manifestations in vivo was tested in swine.

Results The OSCS found in contaminated lots of unfractionated heparin, as well as a synthetically generated OSCS reference standard, directly activated the kinin–kallikrein pathway in human plasma, which can lead to the generation of bradykinin, a potent vasoactive mediator. In addition, OSCS induced generation of C3a and C5a, potent anaphylatoxins derived from complement proteins. Activation of these two pathways was unexpectedly linked and dependent on fluid-phase activation of factor XII. Screening of plasma samples from various species indicated that swine and humans are sensitive to the effects of OSCS in a similar manner. OSCS-containing heparin and synthetically derived OSCS induced hypotension associated with kallikrein activation when administered by intravenous infusion in swine.

Conclusions Our results provide a scientific rationale for a potential biologic link between the presence of OSCS in suspect lots of heparin and the observed clinical adverse events. An assay to assess the amidolytic activity of kallikrein can supplement analytic tests to protect the heparin supply chain by screening for OSCS and other highly sulfated polysaccharide contaminants of heparin that can activate the contact system.

THIS ARTICLE
- Abstract
- PDF
- Supplementary Material

TOOLS & SERVICES
- Add to Personal Archive
- Add to Citation Manager
- Notify a Friend
- E-mail When Cited

MORE INFORMATION
- PubMed Citation

In January 2008, health authorities in the United States began receiving reports of clusters of acute hypersensitivity reactions in patients undergoing dialysis that had been occurring since November 2007. Symptoms included hypotension, facial swelling, tachycardia, urticaria, and nausea. Although initial investigations focused on dialysis equipment, an investigation by the Centers for Disease Control and Prevention identified the receipt of heparin sodium for injection (1000 U per milliliter, in 10-ml and 30-ml multidose vials), manufactured by Baxter Healthcare, as a common feature of the cases.[1] This finding led Baxter Healthcare to recall, on January 17, 2008, nine lots of heparin sodium for injection. As of April 13, 2008, there were 81 reports of death that involved at least one sign or symptom of an allergic reaction or hypotension in patients receiving heparin since January 1, 2007. However, the fact that allergic symptoms or hypotension were reported does not mean that these were the cause of death in all cases.

After this initial recall, there were continuing reports of allergic-type reactions, including some deaths, after injection of bolus heparin not only in patients undergoing dialysis but also in patients in other clinical settings, such as those undergoing cardiac procedures. On February 28, 2008, Baxter Healthcare recalled all remaining lots and doses of its multidose and single-dose vials of heparin sodium for injection and HEP-LOCK heparin flush products. Since that recall, monitoring by the Food and Drug Administration (FDA) has indicated that, in March 2008, the number of deaths reported in association with heparin usage had returned to baseline levels.[2]

However, on March 6, a heparin recall was announced in Germany because of a cluster of reactions in patients undergoing dialysis that were linked to a different manufacturer's heparin. On the same day, the FDA posted descriptions of analytic methods on its Web site and recommended that all manufacturers and regulatory authorities screen for a contaminant in heparin.[3] This screening revealed widespread contamination of the heparin supply in at least 12 countries.

The contaminant was recently identified as an unusual oversulfated form of chondroitin sulfate (OSCS) representing up to approximately 30% wt/wt in suspect lots of heparin; no other contaminants were observed.[4] In addition, dermatan sulfate, a known impurity of heparin, was found in selected samples.

Both heparin and chondroitin sulfate are members of the glycosaminoglycan family of complex polysaccharides; heparin contains a disaccharide repeat unit of glucuronic–iduronic acid linked to glucosamine, and chondroitin sulfate contains a disaccharide repeat unit of glucuronic acid linked to galactosamine. Analysis of the contaminant unexpectedly revealed an unusual type of sulfation not found in any natural sources of chondroitin sulfate and indicated that OSCS, containing four sulfates per disaccharide unit, is structurally similar to heparin (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

However, the biologic link between the presence of the OSCS in heparin and the adverse clinical events remained to be established. Highly charged polyanionic polymers are known to modulate various enzymatic cascades in plasma, affecting coagulation, fibrinolysis, inflammation, and vasculature function.[5,6] Bradykinin, a potent vasoactive peptide mediator, is generated through the activation of the contact system of coagulation, which is initiated upon contact of factor XII with a negatively charged surface in the presence of prekallikrein and high-molecular-weight kininogen. Highly sulfated polysaccharides have been shown to serve as a negatively charged surface that can initiate fluid-phase activation of the contact system.[5,7] However, initial attempts to recapitulate the adverse responses in experimental models were unsuccessful.[8] Without a definitive link between the contaminant and the clinical reactions, concerns remain that the screening tests currently in place may not be adequate to prevent further cases. We therefore set out to identify a biologic basis for a link between OSCS and allergic-type reactions.

Case Report

A representative case involved a 63-year-old woman with a complex medical history, including end-stage renal disease treated with the use of hemodialysis for 7 years, who received heparin intravenously during hemodialysis (5000-U loading dose and 500 U per hour during the procedure) three times weekly. In mid-January 2008, the development of "low blood pressure" was reported, along with nausea and dyspnea, during dialysis. She was treated with normal saline and oxygen (2 liters per minute), and the rates of ultrafiltration and blood flow were slowed. She recovered after 30 minutes, and dialysis was continued. Two days later, she again received intravenous heparin (5000-U loading dose and 500 U per hour) from the same lots of heparin from the same manufacturer (Baxter Healthcare). Immediately after dialysis was initiated, the patient had an anaphylactoid reaction, with a sudden drop in blood pressure (to 65/34 mm Hg), dyspnea, nausea, vomiting, and constitutional symptoms. She was treated with a bolus of normal saline and oxygen (2 liters per minute). Hemodialysis was continued for another hour. The patient continued to feel ill, was admitted to the hospital, and was discharged 2 days later, after recovery. Further dialysis was performed with the use of heparin from another manufacturer.

Methods

Test Samples

Twenty-nine clinical lots of heparin, including 13 associated with clinical adverse events, were procured from the FDA and coded as unknown samples 1 through 29. A laboratory lot of heparin was included as a control. For all analytic and biologic tests, samples were dosed on a weight basis; specific activity of heparin is typically approximately 180 U per milligram. OSCS was purified to homogeneity from a lot of heparin that was known to be contaminated, as previously described.[4] Briefly, OSCS-contaminated heparin was subjected to anion-exchange chromatography followed by alcohol precipitation to isolate the contaminant.[4] The identity of the contaminant was confirmed by means of multiple orthogonal techniques, including multidimensional nuclear magnetic resonance (NMR), enzymatic digestion followed by high-performance liquid chromatography, and liquid chromatography–mass spectrometry.[4] After identification of the contaminant as OSCS, a synthetic standard was generated through chemical sulfonation of chondroitin sulfate A and was exhaustively characterized to ensure authenticity, as previously described.[4] The synthetic OSCS was used in spiking experiments to qualify the analytic procedures (especially one-dimensional proton NMR, described below) to determine limits of detection and to establish accurate quantification.[4] The limit of detection for this assay was determined to be 0.3% on a weight basis for both dermatan sulfate and OSCS.

Analytic Methods

To ensure accurate identification and quantification of any contaminants and impurities, the 29 coded test samples were subjected to orthogonal analytic techniques. Proton NMR, anion-exchange chromatography, and capillary electrophoresis were used to screen the samples for the presence of OSCS, dermatan sulfate, and other nonheparin components. The levels of OSCS and dermatan sulfate were quantified with the use of a 600-MHz NMR instrument to ensure peak resolution. The details of quantification, as well as a representative spectrum, are given in Fig. 1 and Table 1 in the Supplementary Appendix. For samples with unusual patterns, the identity of contaminants or impurities, including OSCS, was confirmed by means of detailed characterization, including the use of multidimensional NMR.[4]

Amidolytic Activity of Kallikrein

Pooled human plasma or factor XII–depleted plasma (American Diagnostica) was treated with various concentrations of coded test samples of heparin, chondroitin sulfate A, or synthetic OSCS for 5 minutes at 37°C. The amidolytic activity of kallikrein (with a small contribution of factor XII)[9] was assessed by adding the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline [pNA]) for 30 minutes at 37°C, followed by spectrophotometric measurement of the absorbance at 450 nM.

Generation of C3a and C5a

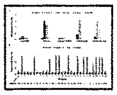
Pooled human EDTA plasma or factor XII–depleted plasma (American Diagnostica) was treated with various concentrations of OSCS-contaminated heparin, control heparin, chondroitin sulfate A, or synthetic OSCS for 30 minutes at 37°C. C3a and C5a activation products of the complement cascade were assayed by means of a sandwich enzyme-linked immunosorbent assay (ELISA), as specified in the manufacturer's instructions (Becton Dickinson and Integrated Biotech Laboratories for C3a and C5a, respectively).

In Vivo Studies

The swine were handled and treated in compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and the federal Animal Welfare Act. The experimental procedures were performed according to the Institutional Animal Care and Use Committee–approved protocol of the Virginia Polytechnic Institute and State University, Blacksburg, Virginia. Domestic Yorkshire crossbred swine were of either sex (Virginia Polytechnic Institute and State University) and ranged in weight from 10 to 25 kg. They were initially anesthetized with an intravenous injection of 6 mg of tiletamine hydrochloride per kilogram of body weight and 2.2 mg of xylazine per kilogram, and then a single-lumen silicone catheter was implanted in the left jugular vein of each animal. Adequate anesthesia was maintained throughout the procedure with the administration of supplemental tiletamine. After a 5-minute stabilization period, each pig received an intravenous bolus infusion of 5 mg of the test substance per kilogram (three to six pigs per test substance). All the pigs were continuously monitored for vital signs with the use of an oscillometric blood pressure monitor (Cardell 9401/9403, CAS Medical Systems) for systolic, diastolic, and mean arterial blood pressures, pulse oximetry for pulse and respiratory rates, and a rectal probe for body temperature. At the end of the 60-minute observation period, the animals were euthanized with the use of an intravenous infusion of Fatal Plus (Vortech Pharmaceuticals) at a dose of 0.22 ml per kilogram. Blood samples were collected at baseline and at 5, 10, 20, 40, and 60 minutes and were kept in 5 mM EDTA. Plasma was isolated after centrifugation at 4°C and flash-frozen on dry ice. Frozen samples were thawed at 4°C and assayed for amidolytic activity of kallikrein with the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-pNA), as described above.

Results

Given the association of activation of the contact system with negatively charged polysaccharides, we sought to elucidate whether an in vitro biologic response could be correlated with the identity or levels of contaminant within heparin lots. To this end, we examined the ability of a sample of OSCS-contaminated heparin, containing 19.3% wt/wt OSCS (Table 1 in the Supplementary Appendix), to activate kallikrein amidolytic activity in human plasma (Figure 1A). The contaminated heparin showed a bell-shaped dose response, which is typical of glycosaminoglycan-mediated responses.[5,10] At 2.5 and 25 µg per milliliter, robust activation of kallikrein was found with the contaminated heparin sample but not with a control sample of uncontaminated heparin. These concentrations are in the range of a clinically efficacious concentration of heparin of approximately 1 to 5 µg per milliliter, based on a specific activity of about 180 U per milligram. High concentrations of the OSCS-contaminated heparin (250 µg per milliliter) induced little or no amidolytic activity of kallikrein, suggesting that at this concentration, heparin may inhibit or cause depletion of factor XII, as previously described.[7,11,12] This high concentration of heparin also prevented activation of the contact system in response to kaolin, a potent activator (data not shown).



View larger version (25K):
[in this window]
[in a new window]
Get PowerPoint Slide ▶

Figure 1. Effect of OSCS on Kallikrein Activity.

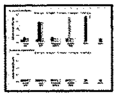
Pooled human plasma samples were treated with control unfractionated heparin (UFH) or OSCS-contaminated heparin (0.025 to 250 µg per milliliter) or with chondroitin sulfate A, synthetic OSCS, or purified OSCS contaminant (0.0025 to 25 µg per milliliter). Amidolytic activity was assessed by the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline); the effect on kallikrein amidolytic activity is shown (Panel A). The presence of OSCS in heparin was associated with the induction of kallikrein activity. Twenty-nine samples of heparin, representing both suspect heparin lots and control lots, were analyzed in a blinded fashion for both the presence of OSCS and the ability to activate kallikrein (Panel B). The presence of OSCS was detected and quantified by one-dimensional nuclear magnetic resonance spectroscopy (see Fig. 2 in the Supplementary Appendix). The percentage of each sample that was OSCS is shown below the plot. Kallikrein amidolytic activity was assessed at various concentrations of heparin; Sample 7 was not analyzed for kallikrein activity owing to the limited quantity available. ND denotes not detectable, and OD optical density.

To further verify that the contaminant was responsible for the activation of the contact system, OSCS was purified to homogeneity by means of anion-exchange chromatography followed by alcohol precipitation. In addition, an OSCS standard was created through chemical sulfonation of chondroitin sulfate A, to form OSCS.[4] The purified contaminant and the OSCS standard were identical, as judged by several orthogonal analytic techniques, including two-dimensional NMR.[4] Both the purified contaminant and the synthetic OSCS showed robust activation of kallikrein activity at 0.25 µg and 2.5 µg per milliliter (Figure 1A). The peak activity of the purified contaminant and the synthetic OSCS standard were observed at a level that was approximately an order of magnitude lower than that found for the contaminated heparin sample. This is consistent with the observation that the OSCS constituted approximately 20% of the contaminated sample. Chondroitin sulfate A showed no induction of amidolytic activity.

These results are in good agreement with the observations of Hojima et al.,[5] who demonstrated that oversulfated chondroitin, but not chondroitin A, B, or C, can activate the kinin pathway. Heparin also activated the contact system in an in vitro model system involving purified protein components[5,13] but did not in plasma,[13] suggesting that negative-regulatory factors present in plasma may prevent activation of the contact system by heparin. One such mechanism is the fact that heparin is known to enhance antithrombin III–mediated inhibition of factor XII. Our results indicate that OSCS, in contrast to heparin but similar to dextran sulfate,[13] can activate the contact system in plasma.

The 29 heparin samples procured from the FDA, consisting of both suspect heparin lots associated with clinical events as well as control heparin lots, were screened in a blinded fashion for both the presence of OSCS and the ability to activate the contact system (Figure 1B). There was complete correspondence between the presence of detectable amounts of OSCS by one-dimensional proton NMR and the ability of a sample to induce robust amidolytic activity of kallikrein (Figure 1B). The biologic activity was generally characterized as an all-or-none response, with all 13 samples containing detectable levels of OSCS having a positive response at 25 µg or 2.5 µg per milliliter. Sample 11, which contained the highest level of contaminant (27.4%), also showed activity at 0.25 µg per milliliter, whereas Sample 25, which contained the lowest level of contaminant (2.4%), showed only modest activity at 2.5 µg per milliliter. In contrast, there was no association between the level of inducible kallikrein activity and the level of dermatan sulfate (Fig. 2 in the Supplementary Appendix), an impurity found in many heparin preparations.

Direct activation of the contact system by the contaminated heparin and the synthetic OSCS standard was confirmed through the use of human plasma depleted of factor XII, the upstream activator of prekallikrein[14] (Figure 2). The contaminated heparin, the synthetically derived OSCS, and the positive control (the kaolin-containing reagent) all failed to induce the amidolytic activity of kallikrein in factor XII–deficient plasma.

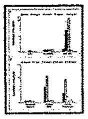


View larger version (20K):
[in this window]
[in a new window]
Get PowerPoint Slide ▶

Figure 2. OSCS-Induced Activation of Kallikrein in Normal or Factor XII–Depleted Plasma.

Control unfractionated heparin (UFH), OSCS-contaminated UFH, chondroitin sulfate A, and synthetic OSCS were incubated with normal plasma (Panel A) or with factor XII–depleted plasma (Panel B); OSCS-induced activation of kallikrein is dependent on factor XII, as indicated. Kaolin-containing buffer was evaluated as a positive control activator of the contact system. Buffer alone was included as a negative control. Amidolytic activity was assessed by the addition of the S-2302 chromagenic substrate (D-Pro-Phe-Arg-p-nitroaniline). OD denotes optical density.

We next examined the ability of contaminated heparin to generate C3a and C5a, potent anaphylatoxins derived from complement proteins. Exposure of human plasma to the contaminated heparin, but not to control heparin, induced the production of C5a (Figure 3). OSCS-induced C5a generation showed a bell-shaped dose response similar to that found for kallikrein activation. Peak C5a activity was observed at 50 µg and 5 µg per milliliter of heparin containing 19.3% OSCS. At 500 µg per milliliter, significant generation of C5a was not observed. Similar results were obtained with the purified OSCS isolated from contaminated heparin and the synthetic OSCS standard, but not with chondroitin sulfate A.

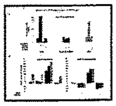


View larger version (19K):
[in this window]
[in a new window]
Get PowerPoint Slide ▶

Figure 3. OSCS and the Generation of Complement-Derived C5a Anaphylatoxin in Human Plasma.

OSCS-contaminated unfractionated heparin (UFH) and control UFH (0.5 to 500 µg per milliliter) (Panel A) or chondroitin sulfate A, synthetic OSCS, and purified OSCS contaminant (0.005 to 50 µg per milliliter) (Panel B) were incubated with normal plasma anticoagulated with EDTA. The generation of C5a was assessed by ELISA.

Surprisingly, the generation of C5a by OSCS-contaminated heparin was more robust in the presence of EDTA, a Ca^{2+}- and Mg^{2+}-chelating agent, than in the absence of EDTA. The classic and alternative pathways of complement activation are known to be dependent upon Ca^{2+} and Mg^{2+}, respectively. As expected, EDTA blocked C3a and C5a generation in response to zymosan, a potent activator of the alternative pathway (Figure 4). These results suggested the possibility that OSCS induces the generation of C3a and C5a in a manner that bypasses the C3 and C5 convertases. To determine whether the generation of C3a and C5a was linked to the activation of the contact system, we next examined C3a and C5a generation in factor XII–depleted plasma (Figure 4). As expected, zymosan induced the generation of C3a and C5a in factor XII–depleted plasma, and this activity was inhibited by EDTA. In contrast, neither C3a nor C5a was generated in factor XII–depleted plasma activated with OSCS, suggesting that OSCS bypasses the normal pathways for complement activation in a manner that is dependent on contact activation through factor XII. The generation of C5a could be restored by reconstituting the factor XII–depleted plasma with purified factor XII (Figure 4A). This finding is further supported by the observation that C5a generation induced by OSCS-contaminated heparin can be inhibited by aprotinin, a protease inhibitor of kallikrein but not of factor XIIa (Figure 4A). Crosstalk between the contact system and the complement cascade has been suggested previously.[15,16,17,18] For example, factor XII has been shown to activate the classical pathway by activating C1.[15] It has also been proposed to substitute for factor D in activating the alternative pathway.[16] However, in these cases, activation of the complement cascade still occurs through divalent cation–dependent pathways. Kallikrein has been shown to act directly on C5 to generate C5a-like biologic activity.[17] Both kallikrein and factor XII can activate the plasminogen pathway leading to the activation of plasmin, which has also been implicated in complement activation.[18] Preliminary data suggest that OSCS is unable to induce C5a generation in plasminogen-depleted plasma (data not shown).



View larger version (21K):
[in this window]
[in a new window]
Get PowerPoint Slide ▶

Figure 4. OSCS Induction of Complement-Derived C3a and C5a Anaphylatoxins and Its Relationship to the Contact System.

Factor XII–depleted plasma was incubated with chondroitin sulfate A, OSCS, or control buffer in the presence or absence of 5 mM EDTA, zymosan (1 mg per milliliter), or aprotinin (400 IU per milliliter) (Panel A). Specific samples were reconstituted with purified factor XII, as indicated. Normal human plasma or factor XII–depleted plasma was incubated with chondroitin sulfate A, OSCS, or control buffer in the presence or absence of 5 mM EDTA, zymosan (1 mg per milliliter), or both (Panel B). C3a and C5a generation was assessed by means of enzyme-linked immunosorbent assay (ELISA).

To identify an appropriate species for in vivo testing of OSCS, a panel of plasma samples were screened for amidolytic activity in response to OSCS-contaminated heparin (Figure 5A). Only swine plasma supported robust amidolytic activity of kallikrein in response to kaolin and OSCS-contaminated heparin but not control heparin. In contrast, rabbit, horse, and rat plasma showed moderate-to-robust amidolytic activity in response to kaolin but not to OSCS-contaminated heparin. These findings are consistent with a report that initial attempts to provoke an allergic response with suspect lots of heparin were unsuccessful.[8] Similarly, we found that rabbits treated with 5 mg of intravenous OSCS-contaminated heparin per kilogram showed no change in temperature, blood pressure, or heart rate as compared with rabbits treated with control heparin (data not shown). Wiggins[19] demonstrated previously that dextran sulfate can induce hypotension in rabbits, but only at a high dose (20 mg per kilogram) and in a manner independent of complement or kinin activation. In contrast, moderate doses of dextran sulfate (5 mg per kilogram) induced a robust hypotensive response in pigs that was dependent on activation of the contact system.[20]

View larger version (29K):
[in this window]
[in a new window]

Get PowerPoint Slide ▶

Figure 5. In Vitro and In Vivo Activity of OSCS.

Human, rat, rabbit, pig, and horse plasma samples were incubated with various concentrations of OSCS-contaminated unfractionated heparin (UFH) or control UFH (Panel A). Kaolin-containing buffer was tested as a positive control. Buffer alone was included as a negative control. Kallikrein amidolytic activity was assessed by the addition of the S-2302 chromogenic substrate; OSCS induces hypotension and kallikrein activity in swine (Panels B and C). Anesthetized Yorkshire crossbred pigs (three to six pigs per group) were treated with a single intravenous bolus (5 mg per kilogram) of control UFH, OSCS-contaminated UFH, chondroitin sulfate A, or synthetic OSCS. Representative data for the heart rate, the mean arterial pressure, the systolic blood pressure, and the diastolic blood pressure are shown (Panel B). EDTA-anticoagulated plasma was collected at baseline and at 5, 10, 20, 40, and 60 minutes after infusion of test samples (Panel C). OD denotes optical density.

To test the in vivo activity of OSCS, pigs were treated with a single intravenous dose (5 mg per kilogram) of OSCS-contaminated heparin, control heparin, synthetic OSCS, or chondroitin sulfate A and were monitored for 60 minutes. Animals treated with control heparin and those treated with OSCS-contaminated heparin showed similar anti-Xa activity during the entire 60-minute observation period (activity at 5 minutes, approximately 3 to 4 IU per milliliter) (Fig. 4 in the Supplementary Appendix). Animals treated with chondroitin sulfate A or synthetic OSCS showed no anti-Xa activity. These results suggest that any anticoagulant activity of OSCS is mediated through a non–antithrombin III–dependent mechanism. Two of six animals treated with OSCS-contaminated heparin had at least a 30% drop in blood pressure over the first 30 minutes after infusion (Figure 5B). One animal remained in a hypotensive state for more than 15 minutes. In contrast, none of the four animals treated with control heparin showed any substantive changes in blood pressure. The adverse events were more severe in pigs treated with the synthetic OSCS, a result consistent with the greater exposure to OSCS in animals treated with pure OSCS as compared with contaminated heparin containing approximately 20 to 30% OSCS. All three pigs treated with synthetic OSCS showed a profound drop in blood pressure (maximal decrease, 45 to 59%) and a concurrent increase in heart rate within minutes after infusion. One animal had difficulty breathing and became cyanotic after a precipitous drop in blood pressure. The heart rate of a second animal increased from 114 beats per minute to 196 beats per minute within 4 minutes after the infusion of OSCS. The third pig showed a transient but pronounced spike in heart rate with a corresponding drop in blood pressure (Figure 5B). In contrast, none of the three pigs treated with chondroitin sulfate A showed any significant changes in blood pressure or heart rate within the first 30 minutes after drug infusion. Thus, intravenous infusion of OSCS is capable of recapitulating the hallmark cardiovascular features of the reaction in swine. The changes in physiological parameters were mirrored by rapid induction of the amidolytic activity of kallikrein (Figure 5C). Kallikrein activity remained high throughout the observation period, even after the vital functions returned to normal, suggesting depletion of high-molecular-weight kininogen and inactivation of bradykinin by kininases in vivo, as previously shown with dextran sulfate.[20] Induction of kallikrein activity was evident in all animals that received OSCS-contaminated heparin, even when no substantive changes in blood pressure were observed. These findings suggest that activation of kallikrein does not always manifest as clinical symptoms, perhaps because of individual variation in control mechanisms that regulate bradykinin activity. Nonetheless, these results also suggest that swine may be an appropriate species in which to assess the potential consequences of OSCS contaminant in cardiovascular and dialysis models as well as in heparin-coated devices.

Discussion

The recent reports of allergic-type serious adverse events in patients receiving heparin and the subsequent detection of widespread contamination have caused intense international concern about the safety of this essential drug. Urgent problems included an immediate and unknown risk to patients' lives, a threat to the supply of a widely used, essential drug, and the need for international cooperation in managing the integrity of a global supply chain. This crisis necessitated an urgent need to both understand the basis for these clinical events and to prevent future occurrences. The development of an analytic assay for OSCS, coupled with the rapid response of manufacturers and regulatory authorities around the world, has undoubtedly limited the harm. However, in the absence of a biologic link between the OSCS contaminant and the adverse events, the adequacy of screening heparin lots to prevent a recurrence is a concern.

Determining whether a link exists between the presence of OSCS and a biologic response required the convergence of two distinct analyses. First, there was a requirement to develop analytic techniques of sufficient sensitivity and specificity to ensure accurate identification and quantification of contaminants or impurities that are present within heparin. Second, there was a requirement to develop a sensitive, clinically appropriate biologic test to determine at what levels, if any, the OSCS would have relevant biologic activity.

With regard to the analytic techniques, a tiered approach was required to ensure effective translation to biologic characteristics. Screening methods were developed to rapidly identify whether heparin lots were contaminated or impure. Then, methods were further developed to enable quantification of the contamination levels. Finally, more sophisticated techniques, such as multidimensional NMR, enabled complete characterization of the contaminant or impurity. This tiered approach was necessitated by the fact that heparin is a polydisperse mixture of glycosaminoglycan chains; orthogonal techniques were therefore required to ensure capture of the other nonheparin components.

Here, we demonstrate that the OSCS present in suspect heparin lots, as well as a synthetic OSCS standard, can directly activate the contact system and induce the generation of C3a and C5a anaphylatoxins in vitro. Moreover, OSCS activates kallikrein in vivo and can induce a profound hypotensive response in pigs, thus providing a potential biologic link between the contaminant and the anaphylactoid reactions seen in affected patients. The finding that hypotension did not develop in all animals treated with OSCS-contaminated heparin, even at a relatively high dose, is consistent with the observation that the majority of patients who received contaminated heparin did not experience an adverse event. However, it is important to note that all animals treated with OSCS-contaminated heparin showed evidence of kallikrein activation in vivo, even in the absence of clinical signs. Patients undergoing dialysis who are also receiving heparin therapy are already at high risk for hypotension because of their exposure to the dialysis membrane, which can also activate the contact system, and their treatment with angiotensin-converting–enzyme inhibitors, which inhibit bradykinin degradation. Exposure to OSCS-contaminated heparin may further increase the risk and could potentially trigger an adverse event. Finally, these findings also suggest that a simple in vitro bioassay could complement the previously described analytic tests[4] to help protect the global supply chain of heparin, by allowing the screening of heparin lots for the presence not only of OSCS but also of other polysulfated contaminants that may have unintended pharmacologic consequences.

Supported by the National Institute of General Medical Sciences (grant GM57073, to Dr. Sasisekharan).

Drs. Kishimoto, Ganguly, Lansing, Zhao, Galcheva-Gargova, Roy, Shriver, and Venkataraman, Mr. Smith, and Mr. Baily reporting being employees of Momenta Pharmaceuticals and holding equity in the company, which has technology on the analysis and characterization of complex mixtures, including heparin. Drs. Sasisekharan and Langer report receiving consulting fees from Scientific Protein Labs and Momenta Pharmaceuticals and holding equity in Momenta Pharmaceuticals. Dr. Austen reports receiving consulting fees from Momenta Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

We thank Dr. Allen P. Kaplan for helpful discussions; Pete Jobst, Animal Resource Manager, and Andrea Aman, Animal Care Technician, at the Virginia–Maryland Regional College of Veterinary Medicine for their excellent technical help during the in vivo experiments; and Ms. Alison Long, Mr. Chris Honan, Dr. Cedric Hubeau, and the staff of the Massachusetts Institute of Technology Division of Comparative Medicine for help with the animal studies.

Source Information

From Momenta Pharmaceuticals (T.K.K., T.G., S.S., J.C.L., G.Z., Z.G.-G., G.S.B., S.R., Z.S., G.V.) and the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Koch Institute for Integrative Cancer Research (K.V., Z.S., R.S.L., G.V., R.S.) — both in Cambridge, MA; Virginia–Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg (S.E., K.P., N.S., T.R.-C.); the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD (A.A.-H., B.F., L.B., M.N., G.J.D.P., J.W.); the Massachusetts Institute of Technology, Cambridge, MA (M.W., J.F.), and Brigham and Women's Hospital and Harvard Medical School, Boston (K.F.A.).

This article (10.1056/NEJMoa0803200) was published at www.nejm.org on April 23, 2008. It will appear in the June 5 issue of the *Journal*.

Address reprint requests to Dr. Sasisekharan at the Department of Biological Engineering, Harvard–MIT Division of Health Sciences and Technology, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Ave., 16-561, Cambridge, MA 02139, or at rams@mit.edu .

References

1. Acute allergic-type reactions among patients undergoing hemodialysis -- multiple states, 2007-2008. MMWR Morb Mortal Wkly Rep 2008;57:124-125. [Medline]
2. Information on adverse event reports and heparin. Rockville, MD: Food and Drug Administration, 2008. (Accessed April 23, 2008, at http://www.fda.gov/cder/drug/infopage/heparin/adverse_events.htm.)
3. Information on heparin sodium injection. Rockville, MD: Food and Drug Administration, 2008. (Accessed April 23, 2008, at http://www.fda.gov/cder/drug/infopage/heparin/default.htm#screening.)
4. Guerrini M, Beccati D, Shriver Z, et al. Oversulfated chondroitin sulfate is a major contaminant in heparin associated with adverse clinical events. Nat Biotechnol (in press).
5. Hojima Y, Cochrane CG, Wiggins RC, Austen KF, Stevens RL. In vitro activation of the contact (Hageman factor) system of plasma by heparin and chondroitin sulfate E. Blood 1984;63:1453-1459. [Free Full Text]
6. Henry SP, Giclas PC, Leeds J, et al. Activation of the alternative pathway of complement by a phosphorothioate oli-gonucleotide: potential mechanism of action. J Pharmacol Exp Ther 1997;281:810-816. [Free Full Text]
7. Silverberg M, Diehl SV. The autoactivation of factor XII (Hageman factor) induced by low-Mr heparin and dextran sulphate: the effect of the Mr of the activating polyanion. Biochem J 1987;248:715-720. [ISI][Medline]
8. Baxter provides update on the heparin investigation. Deerfield, IL: Baxter, March 19, 2008. (Accessed April 23, 2008, at http://www.baxter.com/products/biopharmaceuticals/downloads/heparin_03-19-08.pdf.)
9. Silverberg M, Dunn JT, Garen L, Kaplan AP. Autoactivation of human Hageman factor: demonstration utilizing a synthetic substrate. J Biol Chem 1980;255:7281-7286. [Free Full Text]
10. Verhamme IM, Bock PE, Jackson CM. The preferred pathway of glycosaminoglycan-accelerated inactivation of thrombin by heparin cofactor II. J Biol Chem 2004;279:9785-9795. [Free Full Text]
11. Stead N, Kaplan AP, Rosenberg RD. Inhibition of activated factor XII by antithrombin-heparin cofactor. J Biol Chem 1976;251:6481-6488. [Free Full Text]
12. Olson ST, Sheffer R, Francis AM. High molecular weight kininogen potentiates the heparin-accelerated inhibition of plasma kallikrein by antithrombin: role for antithrombin in the regulation of kallikrein. Biochemistry 1993;32:12136-12147. [CrossRef][ISI][Medline]
13. Pixley RA, Cassello A, De La Cadena RA, Kaufman N, Colman RW. Effect of heparin on the activation of factor XII and the contact system in plasma. Thromb Haemost 1991;66:540-547. [ISI][Medline]
14. Kaplan AP, Austen KF. A prealbumin activator of prekallikrein. II. Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin. J Exp Med 1971;133:696-712. [Abstract]
15. Ghebrehiwet B, Silverberg M, Kaplan AP. Activation of the classical pathway of complement by Hageman factor frag-ment. J Exp Med 1981;153:665-676. [Free Full Text]
16. DiScipio RG. The activation of the alternative pathway C3 convertase by human plasma kallikrein. Immunology 1982;45:587-595. [ISI][Medline]
17. Wiggins RC, Giclas PC, Henson PM. Chemotactic activity generated from the fifth component of complement by plasma kallikrein of the rabbit. J Exp Med 1981;153:1391-1404. [Free Full Text]
18. Schaiff WT, Eisenberg PR. Direct induction of complement activation by pharmacologic activation of plasminogen. Coron Artery Dis 1997;8:9-18. [Medline]
19. Wiggins RC. A different cleavage site for high molecular weight kininogen in vivo following intravenous injection of dextran sulfate in the rabbit. Circ Res 1986;58:595-604. [Abstract]
20. Siebeck M, Cheronis JC, Fink E, et al. Dextran sulfate activates contact system and mediates arterial hypotension via B2 kinin receptors. J Appl Physiol 1994;77:2675-2680. [Free Full Text]

Agreement between the Department of Health and Human Services of the United States of America and the State Food and Drug Administration of the People's Republic of China on the Safety of Drugs and Medical Devices

The Department of Health and Human Services ("HHS") of the United States of America ("United States") and the State Food and Drug Administration ("SFDA") of the People's Republic of China ("China") (hereinafter referred to together as "the Parties"):

Understanding the mutual benefits of protecting the public health through improved cooperation between the Parties with regard to monitoring and regulating the safety of drugs and medical devices;

Desiring to work together to better ensure the safety and quality of Drugs, Excipients, and Medical Devices; and

Recognizing that such cooperation can improve the health of the citizens of both the United States and China and enhance confidence in the regulation of Drugs, Excipients, and Medical Devices in both countries;

Have agreed as follows:

Article I Purpose

The purpose of this Agreement is to establish methods of cooperation between the Parties that will provide the Food and Drug Administration within HHS ("HHS/FDA") with additional information about products exported from the customs territory of China to the United States, provide SFDA with increased sharing of information about products exported from the United States to China, and encourage further regulatory cooperation between the Parties regarding Drug and Medical Device regulation.

Article II General Principles

A. The Parties shall engage in regulatory cooperation regarding the export of Drugs, Excipients, and Medical Devices from the customs territory of China to the United States and Drugs, Excipients, and Medical Devices produced in the United States and exported to the customs territory of China as set out in Article VI and as further defined in Work Plans to be agreed upon by the Parties.

B. The Parties shall engage in information-sharing to improve their mutual understanding of, and to gain greater confidence in, each Party's regulatory system as set out in Article V and as further defined in Work Plans to be agreed upon by the Parties. As specified in Article V, each Party shall share relevant information with the other Party, including on relevant laws, regulations, areas of jurisdiction, and public health and safety.

C. The Parties shall engage in regulatory cooperation regarding improving the authenticity, quality, safety, and effectiveness of Drugs, Excipients, and Medical Devices as set out in Articles IV and VI and as further defined in Work Plans to be agreed upon by the Parties.

The Parties shall commit to annual meetings between senior Agency leaders to discuss and evaluate progress under this Agreement, among other things.

Article III Definitions

For purposes of this Agreement the following definitions shall apply:

A. "API" or "Active Pharmaceutical Ingredient" means any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

B. "Counterfeit Drugs and Medical Devices" means a product that is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to branded and generic products and may include products with correct ingredients, with wrong ingredients, without active ingredients, with incorrect quantity of active ingredient, or with fake packaging.

C. "Designated Drugs and Designated Medical Devices" means a Drug (including APIs) and Excipients or Medical Device, respectively, designated for inclusion in each phase of implementation, based on criteria established in Article IV. A.

D. "Drug" means any material commonly used for human pharmaceutical use. The term includes the following materials:
   1. Finished-dosage forms (including both over-the-counter ("OTC") and prescription drugs);
   2. Drug substance, or active pharmaceutical ingredients ("APIs");
   3. Biologic drugs (e.g., vaccines and monoclonal antibodies); and
   4. Products taken by mouth intended to supplement the diet that:
      (i) bear or contain one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use in humans to supplement the diet by increasing the total dietary intake; ora concentrate, metabolite, constituent, extract or combination of any of the above; and
      (ii) meet any one of the following characteristics:
         - are not clearly labeled as dietary supplements; or
         - contain claims to diagnose, cure, mitigate, treat, or prevent disease; or
         - contain substances that are regulated by HHS/FDA as APIs.

E. "Excipient" means any components other than APIs that are commonly used in a pharmaceutical product. These components may include vehicles and additives, such as dyes, flavors, binders, emollients, fillers, lubricants, and preservatives.

F. "Firm" means any business within the customs territory of China or within the United States that is engaged in the manufacture (including processing) and distribution (including export) of Drugs, Excipients, and Medical Devices.

G. "HHS/FDA Requirements" means any U.S. laws, regulations or other requirements, including any amendment adopted after the date of entry into force of this Agreement, concerning Drugs, Excipients, and Medical Devices that are administered or enforced by HHS/FDA.
"SFDA Requirements" means any Chinese laws, regulations or other requirements, including any amendment adopted after the date of entry into force of this Agreement, concerning Drugs, Excipients, and Medical Devices that are administered or enforced by SFDA.

H. "Medical Device" means any instrument, apparatus, machine, implant, *in vitro* reagent, or similar or related article, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in humans, or intended to affect the structure or any function of the human body, and which is not a drug.

I. "SFDA-Registered Firm" means a Firm that SFDA has determined meets SFDA Requirements and that is registered with SFDA.
"HHS/FDA Registered Firm" means a firm that complies with U.S. registration and listing requirements and that is registered with HHS/FDA.

J. "Facility" means any Firm's site within the customs territory of China or in the United States that is engaged in manufacturing, producing, processing, packing, testing, holding, transporting, distributing, or exporting Drugs, Excipients, and Medical Devices.

Article IV Import/Export Tools

A. Determination of Designated Drug and Designated Medical Devices

This Article will be implemented in a phased approach, beginning with a defined list of Designated Drugs and Designated Medical Devices. The Parties shall conduct a formal evaluation of the implementation of this Article for the products designated in paragraph 2 at the conclusion of the 12-month period described in Article VII.D and annually thereafter. Based on the Parties' determination of the success of this program, the Parties may agree to add or delete specific Drugs, Excipients, and Medical Devices. Timing for the evaluation will be established through the Work Plan.

1. *Factors.* The Parties shall consult on the designation of which products to include in each phase, as appropriate, based on the following factors:
    a. potential or actual, direct or indirect risk to the public health associated with the product, based on testing, inspection results or other relevant information;
    b. the rate of refusal of admission in either Party's country or of problems associated with the product before, during or after entering the domestic commerce of the other Party's country, including product recalls, safety alerts and enforcement actions;
    c. fraudulent or deceptive labeling or indications of any substitution or additions of a substance to a product or an ingredient of a product that reduces the quality of the ingredient or product or makes it appear of greater value than it is, without clearly revealing such substitution or addition to the recipient in the importing country;
    d. promotion or advertising of products intended for consumers of the importing country, beyond the products' approved indications for use; and
    e. the feasibility of implementing an effective and timely Work Plan with respect to the product.
2. *First Phase – Designated Drugs and Designated Medical Devices.*
The Parties agree that the first phase shall include products designated by each Party. Designated Drugs shall include any substance or chemical that may be used as an API for any Designated Drug under this Agreement, even if the entity manufacturing or distributing the substance or chemical does not identify the product as an API. Details on these designations shall be determined through the Work Plan. Designated Drugs and Designated Medical Devices shall include:
    a. SFDA-Designated Drugs:
        i. Recombinant Human Insulin
        ii. Lysine Fat and Lysine Salt
        iii. Cefoperazone and its salts
        iv. Paclitaxel injection
        v. Penicillin and its finished dosage form
        vi. Diagnostic kit for blood screening, specifically, for HIV/AIDS and Hepatitis B & C

- b. SFDA-Designated Medical Devices:
  - i. Intraocular Lenses
  - ii. Cardiac pacemakers
- c. HHS/FDA-Designated Drugs:
  - i. Gentamicin sulfate
  - ii. Atorvastatin
  - iii. Sildenafil
  - iv. Dietary supplements intended for erectile dysfunction or sexual enhancement
  - v. Human Growth Hormone
  - vi. Oseltamivir
  - vii. Cephalosporins manufactured in facilities that also manufacture non-cephalosporin drugs
  - viii. Glycerin
- d. HHS/FDA-Designated Medical Devices:
  - i. Glucose test strips
  - ii. Condoms

B. Registration and Collaboration on Designated Drugs and Designated Medical Devices

1. With respect to Designated Drugs and Designated Medical Devices:
   - a. For those designated by HHS/FDA, SFDA shall require that all Firms that manufacture Designated Drugs and Designated Medical Devices intended for export to the United States are registered by SFDA.
   - b. For those designated by SFDA, HHS/FDA shall provide SFDA with the following available information as agreed to in the Work Plan:
     - i. the facilities that manufacture the products;
     - ii. information from the product approval or clearance package;
     - iii. recalls, warning letters, and enforcement actions; and
     - iv. reported post-marketing adverse events
2. HHS/FDA shall consult with SFDA to assist SFDA in understanding HHS/FDA Requirements for Designated Drugs and Designated Medical Devices.
3. HHS/FDA and SFDA shall review the HHS/FDA Requirements for the Designated Drugs and Designated Medical Devices and the SFDA Requirements for the Designated Drugs and Designated Medical Devices to understand the differences and identify the means to ensure the quality, safety, and authenticity of Designated Drugs and Designated Medical Devices, given different regulatory systems.
4. SFDA shall maintain documents on file related to reviews, inspections, testing, recalls, compliance, and any other assessment of a Firm of Designated Drugs and Designated Medical Devices. SFDA shall make such records available to HHS/FDA within 7 work days of an HHS/FDA request.

C. Future Collaboration on Registration and Certification

The Parties agree to pursue activities to better understand the differences and the gaps between HHS/FDA and SFDA requirements and establish mechanisms to address those gaps. Specifically, SFDA shall actively create conditions to enable SFDA to certify that HHS/FDA Requirements are met for firms producing Designated Drugs and Designated Medical Devices intended for export to the United States. Once these new conditions mature for SFDA, the Parties may agree to modify this Agreement to include provisions that provide for the certification of products, exported from the customs territory of China to the United States, to HHS/FDA requirements, and for appropriate export control mechanisms.

D. Product Integrity and Security

1. The Parties shall cooperate on the establishment of the pedigree (chain-of-custody) systems, as follows, for those Drugs designated under Article IV A. that are identified in the Work Plan as being at risk for counterfeiting;
    a. The Parties shall establish and implement measures, including pedigree requirements, to further ensure the integrity and security of Designated Drugs. The Parties shall collaborate with each other on the establishment of such pedigree requirements for both domestic and exported Designated Drugs.
    b. The Parties shall establish and implement pedigree systems. The pedigree shall include information on Designated Drugs and their manufacturers as follows:

        i. product information (drug name, manufacturer, product registration or identification number);
        ii. item information (unique product serial number, dosage form, strength, container size, lot number, expiration date);
        iii. information about each party to the transaction (including company name, street address, license number, contact person, and telephone number); and
        iv. transaction information (date product was shipped from seller, date received by purchaser).
    d. Each Party shall establish and implement standards for a comprehensive electronic tracking system for each unique package.
2. The Parties shall also work on the following product integrity and security measures for all Drugs:

    a. Each Party shall enhance enforcement against entities that fail to provide a pedigree, provide a false pedigree, or fail to comply with any other provisions related to the integrity or security of Drugs.
    b. Each Party shall develop a program to inform and educate supply-chain stakeholders and the public on how to avoid and minimize their risk of receiving a misbranded, adulterated or Counterfeit Drug or Medical Device, and how to report suspect drugs, excipients, medical devices and suspicious parties.
    c. SFDA and HHS/FDA shall respond rapidly to, and investigate reports of, Drugs, Excipients, and Medical Devices suspected of being misbranded, adulterated, or counterfeited. SFDA and HHS/FDA shall also notify each other of any such reports and the steps they have taken or plan to take to investigate the report. SFDA and HHS/FDA shall also report Counterfeit Drugs to the World Health Organization (WHO).
    d. Each Party shall take steps to adopt and implement regulations and practices (e.g., good distribution practices) and guidelines (e.g., pharmacovigilance, rapid response for counterfeits) consistent with those established by the World Health Organization (WHO) including with respect to Counterfeit Drug identification and prevention, including the enforcement of laws and regulations that encompass APIs, Excipients, and finished-dosage forms misidentified as to source and composition. Details of the collaboration on standards shall be determined through the Work Plan.
    e. Each Party shall endeavor to enhance cooperative activities with its appropriate law-enforcement and regulatory authorities to actively investigate and prosecute individuals or entities that manufacture, sell, distribute, handle, test, trade, or export misbranded, adulterated, or Counterfeit Drugs, Excipients, and Medical Devices. Each Party shall actively participate in the WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT), and the Permanent Forum on International Pharmaceutical Crime (PFIPC).

Article V Information Sharing

The Parties shall exchange information related to Drugs, Excipients, and Medical Devices and their respective regulatory systems concerning Drugs, Excipients, and Medical Devices, on a timeframe and with updates as agreed to in the Work Plan, as follows:

A. A Party may provide information to the other Party in the English or Chinese language.
B. The Parties shall exchange copies of and other relevant information concerning their respective laws and regulations.
C. HHS/FDA and SFDA shall provide each other with copies of all relevant HHS/FDA and SFDA Requirements, updated as appropriate, with respect to Designated Products.
D. Each Party shall provide to the other Party a list of all registered API manufacturers, and the products they manufacture, in its respective country.
E. Each Party shall notify the other Party of serious adverse health consequences or death relating to product safety, manufacturing conditions, recalls, serious adverse event reports, and other instances or the gross deception of consumers. Each Party shall promptly respond to requests from the other Party for information concerning any such risk, including contact information for the Firms or other entities concerned. The Work Plan shall include specific commitments to ensure the timeliness of any such notification or response.
F. HHS/FDA shall work with SFDA to better understand the Global Harmonization Task Force (GHTF) National Competent Authority Reporting (NCAR) program, to support both Parties' actively reporting any serious adverse events that involve medical devices into the NCAR program.
G. Each Party shall notify the other Party of its determination that a shipment of Drugs, Excipients, or Medical Devices has been shipped to the other Party's country, for which there is a reasonable probability that the use of, or exposure to, the product will cause serious adverse health consequences or death. The notification shall:
    1. Be in writing;
    2. Be made within 24 hours of the determination;
    3. Include the reasons for the determination; and
    4. Include, as it becomes available, other information that may assist the other Party to identify the shipment and the supplier.
H. Within 30 calendar days of entry into force of this Agreement, each Party shall provide the other with a list of Firms that manufacture Drugs and Medical Devices in its country and are registered in its country, and the products each Firm manufactures. SFDA shall provide to HHS/FDA the list of Drug, Excipients, and Medical Device manufacturers in the customs territory of China that SFDA has determined to be out of compliance with SFDA Requirements, when such a list becomes available.
I. Within 30 calendar days of a request from HHS/FDA, SFDA shall provide HHS/FDA inspection reports requested by HHS/FDA for SFDA-Registered Firms that manufacture or distribute Drugs, Excipients, or Medical Devices that have been or will be exported to the United States. SFDA shall notify HHS/FDA within 10 calendar days of becoming aware of inspection results that indicate significant deficiencies or fraud associated with firms that manufacture or distribute Drugs, Excipients, or Medical Devices that SFDA determines have been or will be exported to the United States. Once HHS/FDA has addressed any remaining remote access issues, HHS/FDA will grant SFDA access to an electronic database of HHS/FDA inspection results.
J. Each Party shall notify the other Party of any Counterfeit Drug, Excipient, or Medical Device found in its country, including information about the source and distribution.

Article VI Regulatory Cooperation

The Parties shall accomplish the following tasks, as it relates to Drugs, Excipients, and Medical Devices:

A. Develop and set out in the Work Plan specific steps and measures to prevent and control Counterfeit Drugs, Excipients and Medical Devices.

B. Develop appropriate regulatory cooperative activities, including training programs and scientific discussions or cooperation, intended to support the long-term stability and effectiveness of the registration and certification programs. For each training or other cooperative activity that requires travel or other organizational costs, each Party shall bear the cost for its respective participants. Appropriate regulatory cooperative activities may include:
   1. development and coordination of the training programs for Chinese inspectors;
   2. technical exchanges and training relating to the use of Good Clinical Practice (GCP) to ensure the safety of human subjects and the collection of valid clinical data; and
   3. training and exchange on the development of evaluation review methods, inspection techniques, establishment of computer databases, evaluation report standard formats, and the development of technical guidance documents, and laws and regulations.

C. The Parties shall cooperate on the implementation of standards.
   1. The Parties shall develop through the Work Plan details of collaboration on the establishment of internationally-recognized standards. These standards may include:
      a. the International Pharmaceutical Excipients Council's standards for excipients;
      b. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, including ICH Q7A Current Good Manufacturing Practice Guideline for APIs;
      c. Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP Standards for Finished-Dosage Form Pharmaceuticals; and
      d. Global Harmonization Task Force Standards, including ISO 13485 medical device requirements.
   2. Upon request, HHS/FDA shall provide assistance to SFDA regarding internationally-recognized standards.

D. Each Party shall develop a streamlined process for facilitating (e.g., issuing a letter of invitation) an inspection by a Party in the other Party's country no later than 5 calendar days after receipt of such a request from a Party. Such inspection may be conducted with or without providing advance notice (as specified in the request) to the establishment concerned. The performance measure for this activity shall be the number of days that elapse between the Party's request and the other Party's response in facilitating the inspection.

E. Each Party may request the other Party to conduct an investigation regarding any Drug, Excipient, or Medical Device, exported from the other Party's country to the Party's country, that the Party has reason to believe may pose a risk to public health or safety. The Party shall respond to the requesting Party within 3 calendar days of the receipt of the request, informing the requesting Party of its decision on whether or not to conduct an investigation. If the decision is to conduct an investigation, the Party shall notify the requesting Party within 15 calendar days from the decision to conduct the investigation of:
   1. information relating to the source of the health or safety risk;
   2. steps taken to remedy the risk; and
   3. the outcome of any remediation.

   The Work Plan shall set out requirements and performance measures related to investigations under this paragraph.

F. HHS/FDA may fully participate in any annual or other SFDA inspection of any SFDA- or HHS/FDA-Registered Firm in the customs territory in China exporting to the United States.

G. Except in extraordinary circumstances, each Party will observe the following procedures: each Party shall publish on its website(s) all proposed regulations and other measures related to Designated Drugs and Designated Medical Devices and allow a reasonable period of time for all interested parties to submit comments. Each Party shall consider such comments and, at the time final regulations are adopted, address in writing significant, substantive comments received from interested persons during the comment period and explain any substantive revision made to the proposed regulations. Both Parties shall also publish on its website all final regulations and measures related to Designated Drugs and Designated Medical Devices and allow a reasonable amount of time before implementation and enforcement. Both Parties shall also publish all of the information listed above in the relevant government publication (i.e., HHS/FDA, the *Federal Register*). Pending the designation of a single relevant government publication for this purpose in China, SFDA shall ensure its website is kept current, so as to assure transparency in rulemaking.

H. HHS/FDA shall report any science and technology cooperation to the Joint Commission on Scientific and Technological cooperation established under the Agreement Between the Government of the United States of America and the Government of the People's Republic of China on Cooperation in Science and Technology, signed at Washington January 31, 1979.

Article VII Administration

A. Within 15 calendar days of the date of entry into force of this Agreement, each Party shall notify the other Party in writing of its primary points of contact for coordinating all bilateral activities under this Agreement, including coordinating meetings, exchanging information, and sending and receiving notifications.

B. The Parties hereby establish a Working Group. Within 30 calendar days of the date of entry into force of this Agreement, each Party shall identify relevant policy and technical experts of each Party to serve on the Working Group.

C. Within 60 calendar days of the date of entry into force of this Agreement, the Working Group shall hold its first meeting to develop a Work Plan that:

1. further details specific activities each Party shall perform pursuant to this Agreement within the first 12-month period following the date of entry into force of this Agreement and time lines for the completion of each such activity; and
2. includes, as appropriate, performance measures to evaluate the success of each such activity.

D. Within 120 calendar days of the date of entry into force of this Agreement, the Working Group shall finalize the Work Plan for the first 12-month period following the date of entry into force of this Agreement. The Parties shall assess the Work Plan at the conclusion of the 12-month period.

E. For each subsequent 12-month period, the Working Group shall meet to develop a Work Plan that further details specific activities that each Party shall perform pursuant to this Agreement within that period and, as appropriate, that includes performance measures to evaluate the success of each such activity. The Parties shall assess each such Work Plan at the conclusion of the relevant period.

F. The Work Plan for each 12-month period, when adopted by the Parties, shall include binding commitments for the effective and timely implementation of this Agreement. Each Party shall make the Work Plan for the first 12 months, and each subsequent year, publicly available on its respective website.

G. Within 180 calendar days of the date of entry into force of this Agreement, high-level representatives of the Parties shall meet to discuss and review the implementation of and progress under this Agreement and related matters.

H. Thereafter, the high-level representatives of the Parties shall meet on an annual basis to discuss and review the implementation of and progress under this Agreement and related matters. Unless the Parties otherwise agree, the location of these annual meetings shall alternate between the United States and China. The Parties may convene additional technical or program-level meetings on an as-needed basis in any mutually agreeable location.

I. For each provision in this Article, each Party shall notify the other Party within 24 hours of determining it will be unable to meet an agreed-upon deadline, for such reasons as U.S. or Chinese holidays, or for any other reason, and will provide the reason for the delay. The Parties may then agree to modify the timelines and establish a new delivery date. Such notification shall occur through the designated points of contact established as per Article VII.1.

Article VIII Performance Measures

A. The Parties shall evaluate and discuss progress under this Agreement on an annual basis, including the effectiveness of SFDA's registration program established pursuant to the Work Plan. HHS/FDA may base its evaluation of such progress on, among other things, the following:

1. the rate of refusal by HHS/FDA of Drugs, Excipients, and Medical Devices exported from the customs territory of China and offered for import into the United States, as compared to the overall rate of refusal in calendar year 2007 or other relevant period by HHS/FDA of Drugs, Excipients, and Medical Devices exported from the customs territory of China and offered for import into the United States; and
2. the volume, frequency and significance in terms of public health hazard of recalls of Drugs, Excipients, and Medical Devices in the United States, including Counterfeit Drugs and Medical Devices, exported from the customs territory of China and offered for import into the United States as compared to the volume, frequency and significance of such recalls in 2007 or other relevant period.

B. SFDA may base its evaluation of such progress on, among other things, the following:

1. a rate of refusal of Designated Drugs and Designated Medical Devices approved by HHS/FDA offered for import into the customs territory of China, as compared to the overall rate of refusal in the previous calendar year;
2. the overall percentage of Designated Drugs and Designated Medical Devices exported from the customs territory of the United States and offered for import into the customs territory of China that are determined as unqualified based on the supervised sample testing; and
3. the volume frequency, and significance in terms of public health hazard of recall of drugs and medical devices in China, including Counterfeit Drugs and Medical Devices, exported from the United States and offered for import into the customs territory of China as compared to the volume, frequency and significance of such recalls in the previous calendar year.

Article IX Final Provisions

A. Nothing in this Agreement precludes the Government of United States or the Government of China from taking any measure to protect the public health or the citizens of its respective country. HHS/FDA and SFDA affirm that it shall work with its country's national, state, provincial, or municipal bodies, as appropriate, to implement this Agreement fully.
B. Nothing in this Agreement shall be construed to affect the rights or obligations of the United States or China under any other agreement in force between the United States and China.
C. HHS/FDA actions with regard to Drugs, Excipients, and Medical Devices shall be governed by HHS/FDA Requirements and all other existing U.S. laws and regulations.
D. SFDA actions with regard to Drugs, Excipients, and Medical Devices shall be governed by SFDA Requirements and all other existing Chinese laws and regulations.
E. The Parties shall endeavor to resolve any dispute regarding the implementation or interpretation of this Agreement through timely consultations.
F. This Agreement shall enter into force upon signature by both Parties and shall remain in force for a period of two years, unless terminated by either Party. On the last day of the two-year period, and of each subsequent two-year period, the Agreement shall automatically be renewed for another two-year period, unless either Party notifies the other Party that it wishes to terminate

the Agreement at least 60 calendar days prior to the last day of the two-year period. In addition, either Party may terminate the Agreement upon 60 calendar days' written notice to the other Party. The Parties may amend this Agreement at any time by mutual written agreement.

DONE at Beijing, this 11th day of December, 2007, in duplicate in the English and Chinese languages, each text being equally authentic.

FOR THE DEPARTMENT OF HEALTH AND HUMAN SERVICES OF THE UNITED STATES OF AMERICA	*FOR THE STATE FOOD AND DRUG ADMINISTRATION OF THE PEOPLE'S REPUBLIC OF CHINA*

Last revised: March 04, 2008